Original Article

Relationship between circulating miRNA-21, atrial fibrosis, and atrial fibrillation in patients with atrial enlargement

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Background: Atrial fibrosis is a landmark of cardiac remodeling to perpetuate atrial fibrillation (AF), and recent studies have indicated that microRNAs (miRNAs) are essential regulators of multiple cardiovascular disease processes. Herein, we aimed to investigate the relationship between circulating microRNA-21 (miR-21), atrial fibrosis, and AF in patients with atrial enlargement.

Methods: A total of 60 persistent AF patients and 60 matched sinus rhythm (SR) controls were enrolled in the study. We measured their plasma miR-21 levels by using quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Then, each patient underwent transthoracic echocardiography (TTE), while persistent AF patients underwent delayed enhancement magnetic resonance imaging (MRI).

Results: The plasma miR-21 concentrations in the AF group were significantly higher than in the controls, and highly correlated [R=0.689, 95% confidence interval (CI): 0.527 to 0.802; P<0.001] with left atrial (LA) fibrosis measured by delayed enhancement MRI. Receiver operating characteristics (ROC) curve analysis showed that the area under the curve (AUC) of plasma miR-21 to identify AF was 0.813 (95% CI: 0.731 to 0.878). The increasing levels of circulating miR-21 were significantly associated with the higher risk of AF by using logistic regression analysis, even after adjustment for known confounding variables.

Conclusions: Circulating miR-21 highly correlates with the quantification of LA fibrosis by using delayed enhancement MRI and is associated with the risk of persistent AF in patients with LA enlargement.

Keywords: Circulating miRNA-21; atrial fibrosis; atrial fibrillation (AF); atrial enlargement

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Introduction

Atrial fibrillation (AF), one of the most frequent cardiac rhythm disorders, is an independent risk factor for adverse cardiovascular outcomes (1), and some studies have revealed that this is a causal relationship (2,3). In the European Union in 2010, the estimated prevalence of AF was 8.8 million adults, and it is expected to rise to 17.9 million by 2060 (4). Using data from the United States, the estimated incidence of AF was 1.2 million cases in 2010, and this number will ascend to 2.6 million in 2030 (5). Despite remarkable advances in anticoagulant therapy and maintenance of sinus rhythm (SR), AF remains an important cause of heart failure and death (6). Left atrial (LA) fibrosis is a process of excessive extracellular matrix production within the LA myocardium, which is essential to perpetuate AF, as demonstrated in experimental models (7). It is also known that AF can lead to LA fibrosis (8), so the 2 pathologies are intertwined. Delayed enhancement magnetic resonance imaging (MRI) is used

to quantify LA fibrosis, which is associated with the risk of adverse cardiovascular and cerebrovascular outcomes, has important prognostic implications (9). Thus, for the management of AF patients, noninvasive markers that can reflect LA fibrosis would be of great clinical benefit.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by influencing protein translation. Circulating miRNAs have been found to be remarkably stable and detectable, which could be regarded as novel clinical biomarkers for a wide range of cardiovascular diseases including hypertension, myocardial infarction, and heart failure (10). MicroRNA-21 (miR-21) is a miRNA that has been demonstrated to activate atrial fibrosis by regulating matrix metalloproteinase2 (11) and transforming growth factor β receptor III (TGFβRIII) (12) in animal models. In the process of LA fibrosis, miR-21 was overexpressed in cardiac fibroblasts, and increased miR-21 expression correlated positively with atrial collagen content (13). A recent human study showed that circulating miR-21 was associated with myocardial fibrosis in patients with aortic stenosis (14). A previous study reported that circulating miRNA-21 was associated with the risk of AF, but it did not address the role of atrial fibrosis in the association of miRNA-21 and atrial fibrillation (15).

However, there is little evidence regarding the relationship between circulating miR-21, quantitative atrial fibrosis, and the incidence of AF patients.

Thus, the present study aimed to determine the correlation between plasma miR-21 and LA fibrosis as estimated by delayed enhancement MRI, and to evaluate the possibility of plasma miR-21 as novel biomarkers for persistent AF in patients with LA enlargement. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3518).

Methods

Study populations

From 2016 to 2017, 60 persistent AF patients with LA enlargement and 60 matched (age, gender, and concomitant diseases) SR controls with LA enlargement at Beijing Chaoyang Hospital of Capital Medical University in China were enrolled in this study. To adjust the contribution of LA enlargement to the development of AF, we focused on the patients with LA enlargement. The definition of LA enlargement was a LA diameter >3.8 cm in females, or >4.0 cm in males (16). All participants had no history of severe concomitant diseases, including congestive heart failure, stroke, malignant diseases, hepatic failure, and renal failure, and no previous ablation procedure. The data of demographic information, height, weight, and concomitant diseases history were collected. Fasting venous blood was collected for the assessments of total cholesterol (TC) and triglyceride (TG). Each participant underwent scheduled transthoracic echocardiography (TTE), while persistent AF patients underwent delayed enhancement MRI. Then, we extracted data of LA diameter and left ventricular ejection fraction (LVEF) from the TTE report.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Beijing Chaoyang Hospital of Capital Medical University (No. 2016-023) and informed consent was taken from all the patients.

LA fibrosis and delayed enhancement MRI

We equipped two 1.5-Tesla MRI scanners (Magnetom Aera, Siemens Healthcare GmbH, Erlangen, Germany) with customized pulse sequences and imaging protocols. All persistent AF patients underwent delayed enhancement MRI to quantify the degree of LA fibrosis by using the methods described in a previous study (17). With the assistance of a volume-rendering tool in 3D, experts could estimate the extent of LA fibrosis successfully, and categorized LA fibrosis as stage 1 (<10%), 2 (10–<20%), 3 (20–<30%), and 4 (≥30% of the atrial wall) (18).

RNA extraction and quantitative reverse transcription polymerase chain reaction

Fasting venous blood was collected from persistent AF patients and matched SR controls by a tube containing ethylenediamine tetraacetic acid (EDTA). The plasma was separated from the venous blood by centrifugation at 1,000 g for 30 min. Then, the plasma was stored at –80 ℃ until analysis. According to the manufacturer's instructions, RNA was extracted from the plasma using TRIzol (Invitrogen, Carlsbad, CA, USA). Synthetic C. elegans miRNA cel-miR-39 (Qiagen, Hilden, Germany), lacking sequence homology to human miRNA, was used to evaluate the isolation efficiency of plasma miRNAs, as described previously (19). Plasma miR-21 and cel-miR-39 were reverse transcribed using specific primers (TaqMan assays,

Table 1 Characteristics of AF group compared with matched SR group

Variable	AF group (N=60)	SR group (N=60)	P value
Age, years	62.4±1.7	62.8±1.8	0.288
Male/female	24/36	27/33	0.307
BMI, kg/m^2	26.5±3.9	26.9±4.1	0.548
Diabetes	16 (26.7)	10 (16.7)	0.184
Hypertension	21 (35.0)	15 (25.0)	0.232
Hyperlipidemia	17 (28.3)	12 (20.0)	0.286
TC, mmol/L	4.93±1.04	4.50±1.14	0.032
TG, mmol/L	1.89 (1.33, 3.28)	1.56 (1.15, 2.06)	0.016
LA diameter, cm	4.64±0.33	4.56±0.25	0.127
LVEF, %	60.4±3.8	62.8±4.5	0.002
Quantification of LA fibrosis, %	19.6±8.4	–	–
AF by fibrosis stage			
1	12 (20.0)	–	–
2	23 (38.3)	–	–
3	19 (31.7)	–	–
4	6 (10.0)	–	–

Categorical data were represented as n (%), and continuous data were represented as mean ± SD or median (25%th, 75%th). SR, sinus rhythm; AF, atrial fibrillation; TC, total cholesterol; TG, triglyceride; LA, left atrial; BMI, body mass index; LVEF, left ventricular ejection fraction.

Applied Biosystems, Waltham, MA, USA). The plasma miR-21 was normalized to cel-miR-39. In order to ensure that the separation efficiency between the samples was homogeneous, if necessary, the extraction procedure was repeated until the cel-miR-39 cycle threshold was within the range of 23.0±1.0. Quantitative polymerase chain reaction (q-PCR) was used to amplify the complementary DNA (cDNA) products (TaqMan assays, Applied Biosystems).

Statistical analysis

Continuous variables between two groups were compared by Student's *t*-tests or the Mann-Whitney U test. Categorical variables were compared by the chi-square test. Comparison among more than two groups was evaluated by analysis of variance (ANOVA). The correlation between plasma miR-21 and LA fibrosis was calculated using Pearson's correlation analysis and linear regression model. Receiver operating characteristic (ROC) curve analysis was used to assess the performance of plasma miR-21 to identify persistent AF, and the optimal cut-off point was determined by the Youden index. The contribution of miR-21 to the presence of AF was calculated by using logistic regression analysis. A P value <0.05 was considered as statistically significant. The software GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA, USA) and IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) were used for statistical analysis.

Results

The characteristics of patients with LA enlargement are presented in *Table 1*. A total of 60 AF patients with LA enlargement and 60 SR controls were included in the study. The group of AF participants with LA enlargement had a mean age of 62.4±1.7 years, 40% of them were male, and their mean body mass index (BMI) was 26.5±3.9 kg/m^2. Some 26.7% of AF participants with LA enlargement had a history of diabetes, whereas the prevalence was 35.0% for hypertension and 28.3% for hyperlipidemia. There was no significant difference in age, gender, BMI, diabetes, hypertension, hyperlipidemia, and LA diameter between

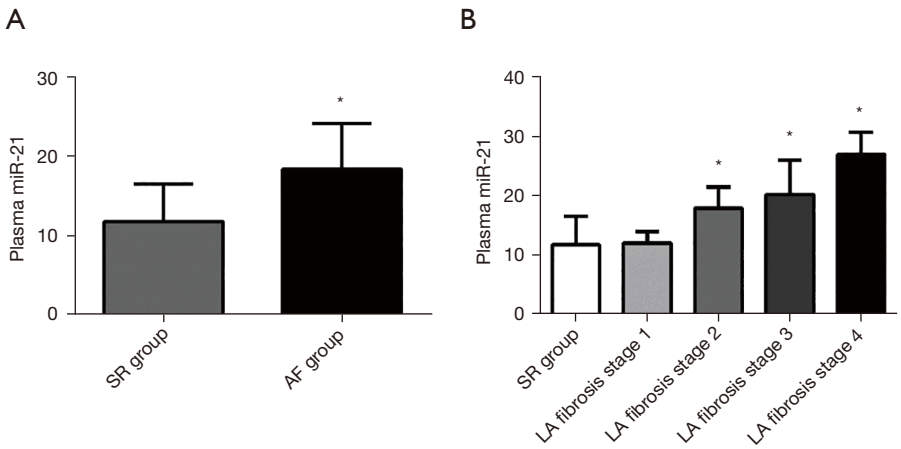

Figure 1 Plasma miR-21 in different groups. (A) The RE level of miR-21 in SR group and AF group; (B) the RE level of miR-21 in SR group and participants with different LA fibrosis stages. *, SR controls *vs.* AF patients, P<0.001; SR controls *vs.* LA fibrosis stage 2, SR controls *vs.* LA fibrosis stage 3, SR controls *vs.* LA fibrosis stage 4, P<0.001. RE, relative expression; SR, sinus rhythm; AF, atrial fibrillation; LA, left atrial.

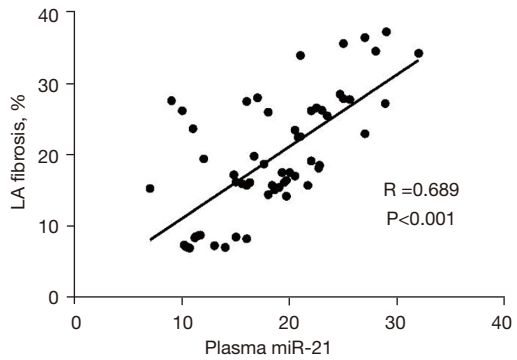

Figure 2 The correlation between LA fibrosis with plasma miR-21 in AF patients. Based on linear regression analysis, LA fibrosis (%) =1.002 × plasma miR-21 +1.193 (R=0.689, 95% CI: 0.527, 0.802; R2=0.474, P<0.001). LA, left atrial; AF, atrial fibrillation; CI, confidence interval.

two groups. Participants with AF had lower LVEF, but higher TC and TG levels than the SR controls. Based on the extent of identified fibrosis from delayed enhancement MRI, the mean level of LA fibrosis was 19.6%±8.4%. The AF group consisted of 12 participants with LA fibrosis stage 1, 23 participants with stage 2, 19 participants with stage 3, and 6 participants with stage 4.

Compared to the SR group with similar characteristics (*Figure 1A*), the circulating miR-21 concentrations in the AF group were significantly higher (AF group: 18.4±5.8; SR group: 11.8±4.7; P<0.001). We further divided AF participants into 4 stages based on the extent of LA fibrosis. Participants from LA fibrosis stage 2 to stage 4 had significantly higher plasma miR-21 concentrations than the controls (P<0.001), while participants with stage 1 had similar miR-21 levels with the controls (*Figure 1B*). As shown in *Figure 1B*, the mean miR-21 circulating levels in LA fibrosis stage 1 was 12.1±1.9, whereas it was 18.0±3.5 in stage 2, 20.3±5.8 in stage 3, and 27.0±3.7 in stage 4.

The circulating miR-21 had a strong and positive linear correlation with LA fibrosis (R=0.689, 95% CI: 0.527 to 0.802; R^2=0.474, P<0.001), and LA fibrosis could be calculated based on the formula: LA fibrosis (%) = 1.002× plasma miR-21 +1.193 (*Figure 2*). It revealed a correlation between miR-21 up-regulation and the level of the LA fibrosis burden.

As shown in *Figure 3*, we sought to determine the performance of plasma miR-21 as a diagnostic biomarker of AF. Circulating miR-21 was a predictor for the incidence of persistent AF by ROC curve analysis, with a sensitivity, specificity, and area under the curve (AUC) of 75.0% (95% CI: 62.1% to 85.3%), 80.0% (95% CI: 67.7% to 89.2%), and 0.813 (95% CI: 0.731 to 0.878), respectively.

Based on the quartile of plasma miR-21, the AF group was divided into 4 levels: <10.5, 10.5–<14.15, 14.15–<19.65, and ≥19.65. Logistic regression analysis suggested that the increasing concentrations of circulating miR-21 was significantly associated with higher risk of AF, even after adjustment for age, gender, BMI, diabetes, hypertension, hyperlipidemia, TC, TG, LA diameter, and

LVEF. Compared with plasma miR-21 <10.5, the odds ratio (OR) of plasma miR-21 ≥19.65 was 1.260 (95% CI: 1.153 to 1.376) for the presence of AF (P<0.001) (*Table 2*).

Discussion

We investigated the role for circulating miR-21 in atrial fibrosis and AF in the scenario of human LA enlargement. The plasma miR-21 concentrations in the AF patients were significantly higher than that in SR controls, and the miR-21 levels were proportional to the extent of LA fibrosis estimated by delayed enhancement MRI. We provided evidence supporting that plasma miR-21 serves as a potential biomarker with high sensitivity and specificity for AF. Circulating miR-21 was shown to be an independent contributing factor for AF, even after adjustment for known confounding variables.

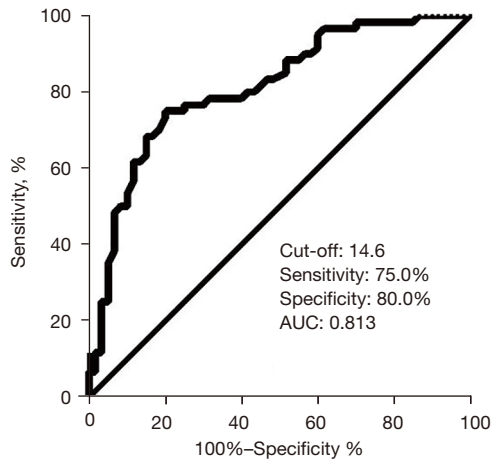

Figure 3 ROC curve analysis for plasma miR-21 as diagnostic biomarker of AF patients. The optimal cut-off point was 14.6, with a sensitivity, specificity, AUC of 75.0% (95% CI: 62.1% to 85.3%), 80.0% (95% CI: 67.7% to 89.2%), 0.813 (95% CI: 0.731 to 0.878). ROC, receiver operating characteristic; AF, atrial fibrillation; AUC, area under the curve; CI, confidence interval.

The expression levels of miR-21 were high in cardiac fibroblasts, which were demonstrated to be involved in the pathogenesis of atrial fibrosis (20). Accumulating data shows that miR21 leads to the development and progress of cardiac fibrosis by regulating several targets, including phosphatase and tensin homologue (PTEN) (11), TGFβRIII (12), and Sprouty 1 (SPRY1) (21). The main mechanism might be the effect of miR-21 on SPRY1, which promotes cardiac fibrosis by inhibition of the extracellular signal-regulated kinases (22). A previous study indicated that upregulation of miR-21 was associated with reduced expression of SPRY1 (21). In addition, the TGF-β signaling pathway is one of the most important promoters of the progression of fibrosis (23). A member of TGFβ superfamily, TGFβRIII could prevent myocardial fibrosis in rat models (24). In a pig model, antimiR-21 was demonstrated to reduce cardiac fibrosis and improve cardiac function (25).

The expression of myocardial miR21 was highly correlated with the level of plasma miR21 (14). In the process of LA fibrosis, miR-21 was overexpressed in cardiac fibroblasts, and miR-21 is secreted into plasma by cardiac fibroblasts. Due to be incorporated in microparticles (exosomes and microvesicles) (26) or associated with RNA-binding proteins (27), plasma miRNA was highly stable and protected from RNase activity, which makes circulating miR-21 a potential clinical biomarker to reflect the extent of LA fibrosis. A recent study revealed that circulating miR-21 was correlated with the degree of LA fibrosis quantified by mapping low-voltage areas (LVAs) in patients undergoing

Table 2 The risk of AF calculated by univariate analysis and multiple logistic regression analysis

Indexes	Plasma miR-21				P value
	1 (<10.5)	2 (10.5–<14.15)	3 (14.15–<19.65)	4 (≥19.65)	
Univariate analysis	1.00 (reference)	1.173 (1.065, 1.241)	1.264 (1.142, 1.355)	1.350 (1.230, 1.455)	<0.001
Model 1	1.00 (reference)	1.162 (1.102, 1.305)	1.235 (1.127, 1.320)	1.332 (1.218, 1.434)	<0.001
Model 2	1.00 (reference)	1.145 (1.087, 1.267)	1.205 (1.102, 1.325)	1.295 (1.187, 1.405)	<0.001
Model 3	1.00 (reference)	1.120 (1.065, 1.245)	1.185 (1.082, 1.277)	1.260 (1.153, 1.376)	<0.001

The model 1 adjusted for age, gender, and BMI. The model 2 adjusted for age, gender, BMI, diabetes, hypertension, hyperlipidemia, TC, and TG. The model 3 adjusted for age, gender, BMI, diabetes, hypertension, hyperlipidemia, TC, TG, left atrial diameter, and LVEF. AF, atrial fibrillation; TC, total cholesterol; TG, triglyceride; LA, left atrial; BMI, body mass index; LVEF, left ventricular ejection fraction.

AF ablation procedures (28). However, LVAs mapping is an invasive procedure and might not be able to be generalized to patients who are unfit to undergo ablation. Delayed enhancement MRI, which was used to quantify LA fibrosis in our study, has been demonstrated as reliable in some multicenter studies (18,29). We found that plasma miR-21 concentration had a high linear correlation with the extent of LA fibrosis measured by delayed enhancement MRI.

The miR-21 is involved in multiple cardiovascular diseases including hypertension, myocardial infarction, and aortic stenosis (14,30). In this study, circulating miR-21 levels in the AF group were higher than in the control group. We also found that increasing concentration of circulating miR-21 was an independent contribution factor to the higher risk of AF by logistic regression analysis. This is consistent with a recent study, which also indicated that circulating miR-21 was associated with ablation procedure outcome in subjects with persistent AF (28). In an animal model, the downregulation of miR-21 nearly abolished the duration of AF by limiting the development of atrial fibrosis (20). A noninvasive method like plasma miR-21, which was found to have high sensitivity and specificity by ROC analysis in our study, could be of important clinical use for identifying persistent AF.

Of note, the role of miR-21 in AF has been controversial until now. In a prospective study, compared with participants without AF, miR-21 concentrations were lower in those with AF (31). This discrepancy might result from different venous blood sample collections, miRNA isolation, and normalization. However, our findings strongly indicated that the circulating miR-21 could be regarded as a clinically measurable risk factor of AF patients that provides evidence on the degree of LA fibrosis.

Our study suggested that the miR-21 could be used as a biomarker, or in conjunction with other clinical, echocardiographic or serological markers to construct a risk profile for atrial fibrosis and AF. However, our study also had several limitations. Multiple human organs including kidney and lung also express miR-21, so we could not distinguish the source of circulating miR-21. However, we tried to decrease the influence of miR-21 from other organs by excluding patients with severe concomitant diseases. Then, the AF patients enrolled in our study were diagnosed with persistent AF rather than paroxysmal AF, so the performance of circulating miR-21 in patients with paroxysmal AF remains unclear. Large sample size and follow-up studies are needed to verify these findings.

In conclusion, our study shows that circulating miR-21 highly correlates with the quantification of LA fibrosis by using delayed enhancement MRI and is associated with the risk of persistent AF in patients with LA enlargement. Plasma miR-21 concentration may be considered a novel biomarker for AF.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3518

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-3518

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3518). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Beijing Chaoyang Hospital of Capital Medical University (No. 2016-023) and informed consent was taken from all the patients.

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