Received: 12 December 2017 | Accepted: 11 January 2018

DOI: 10.1111/anec.12540

ORIGINAL ARTICLE

WILEY

# Fine versus coarse atrial fibrillation in rheumatic mitral stenosis: The impact of aging and the clinical significance

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**Background**: Atrial fibrillation (AF) as the most rhythm disturbance in patients with rheumatic mitral stenosis (MS), is classified in to coarse and fine subtypes according to the height of fibrillatory wave amplitude. The aim of this study is to identify the factors associated with the presence of fine versus coarse morphology in patients with rheumatic MS.

**Methods**: In this cross-sectional study, patients with confirmed diagnosis of severe rheumatic MS admitted between March 2013 and March 2017 were screened. Patients were categorized to sinus rhythm (SR) and AF rhythm (coarse and fine subtypes) groups according to the admission electrocardiogram. The association between various clinical and echocardiographic factors and the development of fine versus coarse AF were examined.

**Results**: Among 754 patients with the diagnosis of rheumatic MS, 288 (198 female) were found to have AF (38%). Among them 206 (71.5%), and 82 (28.5%) patients had fine and coarse morphology respectively. Patient in these two groups were quite similar in terms of echocardiographic parameters and comorbidities. However, patients with fine morphology AF were significantly older. ($p$-Value=.007).

**Conclusion**: Coarse morphology of AF is common in patients with rheumatic MS. While echocardiographic or most clinical parameters do not seem to associate with the occurrence of coarse or fine morphology, age seems to be the only independent factor correlated with the presence of fine subtype of AF in this population.

KEYWORDS
atrial fibrillation, mitral stenosis, mitral valve, rheumatic

## 1 | INTRODUCTION

Rheumatic heart disease (RHD) as a sequela of rheumatic fever continues to be a health concern with a considerable contribution to cardiovascular morbidity, mortality and premature death despite its decreased incidence.(Kumar & Tandon, 2013) Mitral stenosis (MS) is the most frequent valve disease in patients affected by RHD.(Nobuyoshi et al., 2009) Reduction of mitral valve area (MVA) secondary to rheumatic scarring creates an obstruction to the blood flow between the left atrium and the left ventricle, which results in left atrial enlargement and subsequent atrial dysrhythmias. (Pourafkari, Ghaffari, Bancroft, Tajlil, & Nader, 2015).

Atrial fibrillation (AF) is the most common reentry-induced rhythm disturbance in patients with rheumatic MS.(Blackshear, Safford, & Pearce, 1996; Bollmann et al., 2007) Blood stagnation secondary to the contractile dysfunction of atria in AF increases

  

subsequent risk of thromboembolism.(Allessie, Ausma, & Schotten, 2002) Regarding the pathogenesis of developing AF in patients with MS, many factors have been suggested such as age, duration of mitral valve disease, MVA, left atrial size or stress, and the presence of myocardial fibrosis that may lead to a disarray in depolarization vector of the atria.(Holmqvist et al., 2006; Horstkotte, 1992; Josephson, Kastor, & Morganroth, 1977; Kumar & Tandon, 2013) The prevalence of AF in MS patients rises with age as it is 17% among patients in 20s and 30s and increases to 45% during the third decade and reaches to 80% in patients older than 51 years.(Mann, Zipes, Libby, Bonow, & Braunwald, 2015; Vatansever Agca et al., 2008).

AF is subclassified into coarse or fine type based on the presence of F wave amplitudes on surface electrocardiogram (ECG). The presence of the fibrillation F wave amplitude on ECG, indicates a coarse and its absence refers to fine AF (FAF). Besides their different ECG appearance, there are significant variations in the structural integrity and electrical remodeling of the atria depending on the remaining viable atrial myocytes.(Mochalina et al., 2015; Morganroth, Horowitz, Josephson, & Kastor, 1979; Moss, 1984) Atrial activity is more organized in coarse AF (CAF) and it is generally associated with hypertrophy of the atrium muscle mass, while there is significant muscle loss in FAF.(Aysha & Hassan, 1988; Skoulas & Horlick, 1964; Thurmann & Janney, 1962) On the other hand, fine F waves had been proposed to present disorganized atrial activity and structural damage and longer duration and recurrence. (Mochalina et al., 2015; Nault et al., 2009; Nobuyoshi et al., 2009).

Although, the risk of clot formation is probably higher with FAF due to more stagnant flow, thromboembolic events occur more frequently in patients with CAF probably due to some residual mechanical contraction in the left atrial appendage.(Morganroth et al., 1979; Pourafkari et al., 2015) Previous studies have not been consistent regarding association of F wave amplitude and the parameters derived from transesophageal echocardiography such as the chamber size of the left atrium (LA) and ventricle (LV) and the contractile function of the left atrial appendage (LAA)(Mutlu et al., 2003; Nakagawa et al., 2001; Yamamoto et al., 2005). Although MS is considered as a strong risk factor for AF, the parameters associated with the presence of F waves have not been clearly examined and the results have been inconsistent at most.

The purpose of this study was to comparatively describe both clinical and echocardiographic profile of patients with fine and coarse subtypes of AF secondary to rheumatic MS. The primary outcome variable of this study was the mean trans-mitral pressure gradient. We hypothesized that mean trans-mitral gradient in patients with CAF was higher than that measured in those with the fine subtype of AF. We also hypothesized that duration of AF was longer in patients with FAF than those with CAF.

## 2 | METHODS

This retrospective study was conducted between March 2013 and March 2017 on patients with confirmed diagnosis of severe rheumatic MS who were scheduled to undergo a percutaneous balloon mitral valvuloplasty (PBMV) in a university-affiliated heart center. Study Protocol was reviewed and approved by the institutional review board and ethics committee. Informed consent was waived due to the retrospective design of the study; however, all collected clinical data were treated carefully to maintain patient privacy.

Medical charts of patients admitted with the diagnosis of severe rheumatic MS admitted for PBMV in the aforementioned time period were screened for enrollment. Patients with a prior diagnosis of hyperthyroidism, LV ejection fraction below 45%, more than mild aortic stenosis or insufficiency, moderate to severe mitral regurgitation and those with a prior history of any heart surgery were not considered for enrollment. Two cardiologists examined ECG on admission for each patient. Additionally, patients with missing/poor quality admission ECG were excluded.

The study participants were classified as in sinus rhythm (SR) or AF based on their baseline ECG. AF was defined as an irregularly irregular heart rate without any detectable P waves along with fibrillation f waves on 12-lead ECG. Patients with AF were divided into two groups based on the amplitude of F waves in lead V1 on the 12-lead ECG. AF would be classified as coarse "CAF" if the greatest amplitude of F wave was ≥1 mm; and would be categorized as fine AF "FAF" if the F wave amplitude was <1 mm.

We investigated all demographic data and relevant medical history. The studied demographic data included age, gender, smoking habit, history of diabetes mellitus, hypertension, and previous thromboembolic events including cerebrovascular and coronary artery diseases. Moreover, echocardiographic variables such as MVA, mean and peak trans-mitral pressure gradients and pressure half time of mitral valve, left atrial (LA) diameter and volume, LAA emptying flow, LAA filling flow, LV ejection fraction, two-dimensional area of the right atrium (RA), right ventricular systolic pressure (RVSP) and diastolic diameter (RVDD), and Wilkins score measured using transesophageal echocardiography were collected.

Furthermore, the use of oral anticoagulant agents and other medications including digoxin, beta adrenergic blockers, calcium channel blockers, and statin lipid lowering drugs at the time of echocardiographic studies was determined from the available patient records and was entered into the statistical worksheet. All statistical analyses were performed using Statistical Program for Social Sciences (SPSS version 24.0, IBM Inc., Chicago, IL).

All numeric variables were tested using Kolmogorov–Smirnov test for the presence of a normal distribution. Continuous variables with normal distribution were tested with independent t-test and those without a normal distribution were analyzed using a non-parametric Mann–Whitney U test. Normally distributed numerical variables were expressed as mean ± standard deviation (*STD*) and variables without a normal distribution were expressed as median (interquartile range 25th-75th percentiles. Categorical variables were reported as the observed and expected values and were analyzed with chi-square test. For univariate analysis of the categorical variables, the relevant odds ratios (OR) and 95% confidence intervals

(CI) were reported. Age and mean trans-mitral pressure gradients were identified as the only independent variables to be evaluated for their effect on developing FAF with $p$ values <.15, and therefore they were included in a multivariate linear regression model. Receiver operating characteristic curve was also plotted to examine the predictive value of age in the occurrence of FAF. Null hypotheses were rejected with an alpha error <0.05.

## 3 | RESULTS

A total of 930 charts were reviewed from which 754 fulfilled the inclusion criteria. Figure 1 depicts the flow chart of the study design. Among 754 patients with diagnosis of rheumatic MS, 288 (198 female) were found to have AF (38%). Among patients with AF, 82 (28.5%) had CAF. Demographics and characteristics of the study population are shown in Table 1. Accordingly, patients with AF differed from SR group patients in more frequently having hypertension, cerebrovascular, and coronary artery diseases. As expectedly, patients in AF group were more likely to be treated with digoxin, beta-blockers and warfarin anticoagulant. Prevalence of right atrial enlargement was also higher among patients with AF as compared to SR group.

Patients with FAF had a median age of 52 [43–60] and those with CAF had a median age of 48 [38–54] ($p$-value=.007). Compared to the age of 39 [31–47] in the group of patients with sinus rhythm, patients in both groups with atrial fibrillation were significantly older ($P$ < .001). Table 1 illustrates the characteristics of patients in subgroups of FAF and CAF. There was no significant difference in terms of gender, medication and atrial diameters between the two groups. Figures 2 and 3 show the association between various clinical and echocardiographic variables with the presence of FAF/CAF. As depicted, none of the clinical characteristics, echocardiographic variables or medication were different between the two groups. Although similar percentage of patients in both the FAF and CAF were diagnosed with hypertension, diabetes, cerebrovascular, and chronic kidney diseases, a trend for higher prevalence of coronary artery disease was found in patients with FAF.

Additionally, echocardiographic findings with regards to the left and right atrial dimensions, LAA flow velocity, right ventricular dimensions, LV ejection fraction, and Wilkins score did not differ between the two groups. However, trends for higher MVA and mitral valve mean pressure gradient were observed in patients with coarse morphology type of AF (Figure 3). Figure 4 shows the receiver operating characteristic curve for age as a significant contributing factor to the development of FAF. Though significant, it was a poor predictor of FAF; thus, we could not find a cut-off value for age for prediction of presence of FAF versus CAF.

## 4 | DISCUSSION

To date, few studies have assessed F wave morphologies among individuals with predominant rheumatic MS and large proportion

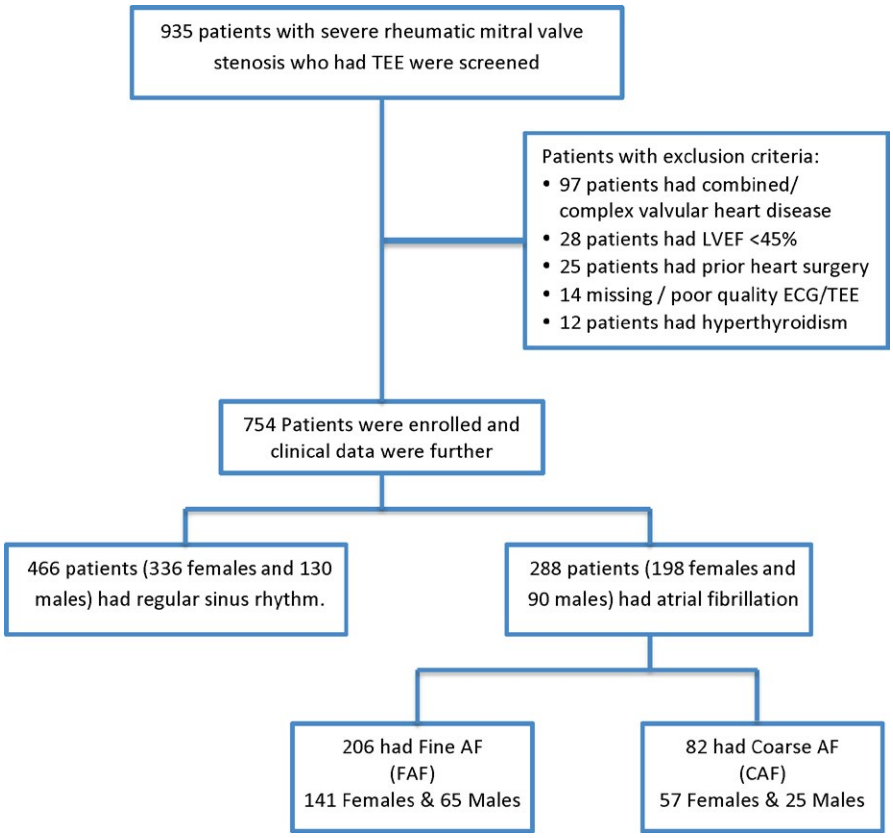


**FIGURE 1** Flow diagram of the patient enrollment with the list of exclusions

**TABLE 1** Comorbid medical conditions and medication history of patients diagnosed with atrial fibrillation based on the presence of coarse f-waves in the electrocardiography

| | Fine Atrial Fibrillation (*N* = 206) | | Coarse Atrial Fibrillation (*N* = 82) | | Sinus Rhythm (*N* = 466) | | |
|---|---|---|---|---|---|---|---|
| | *N* | % | *N* | % | *N* | % | *p*-Value |
| Male | 65 | 29.6% | 25 | 29.3% | 130 | 26.2% | .603 |
| Female | 141 | 68.4% | 57 | 69.5% | 336 | 72.1% | |
| History of Smoking | 17 | 8.3% | 10 | 12.2% | 38 | 8.2% | .474 |
| Hypertension | 25 | 12.1% | 12 | 14.6% | 27 | 5.8% | .003 |
| Diabetes Mellitus | 13 | 6.3% | 3 | 3.7% | 16 | 3.4% | .225 |
| Coronary Artery Disease | 22 | 10.7% | 5 | 6.1% | 12 | 2.6% | <.001 |
| Chronic Kidney Diseases | 1 | 0.5% | 1 | 1.2% | 0 | 0.0% | .109 |
| Cerebrovascular Diseases | 19 | 9.2% | 7 | 8.5% | 15 | 3.2% | .003 |
| Beta Blockers | 21 | 10.2% | 15 | 18.3% | 42 | 9.0% | .039 |
| Digoxin | 18 | 8.7% | 10 | 12.2% | 5 | 1.1% | <.001 |
| Calcium Channel Blockers | 4 | 1.9% | 0 | 0.0% | 3 | 0.6% | .176 |
| Statin Lipid-Lowering Drugs | 6 | 2.9% | 1 | 1.2% | 6 | 1.3% | .307 |
| Warfarin Anticoagulation | 13 | 6.3% | 11 | 13.4% | 10 | 2.1% | <.001 |
| Left Atrial Enlargement | 46 | 22.3% | 29 | 35.4% | 102.0 | 21.9% | .650 |
| Right Atrial Enlargement | 29 | 14.1% | 19 | 23.2% | 19.0 | 4.1% | <.001 |

O: Observed frequencies are shown with percentage of observations: Each subscript letter denotes a subset of AF categories whose column proportions do not differ significantly from each other at the .05 level.

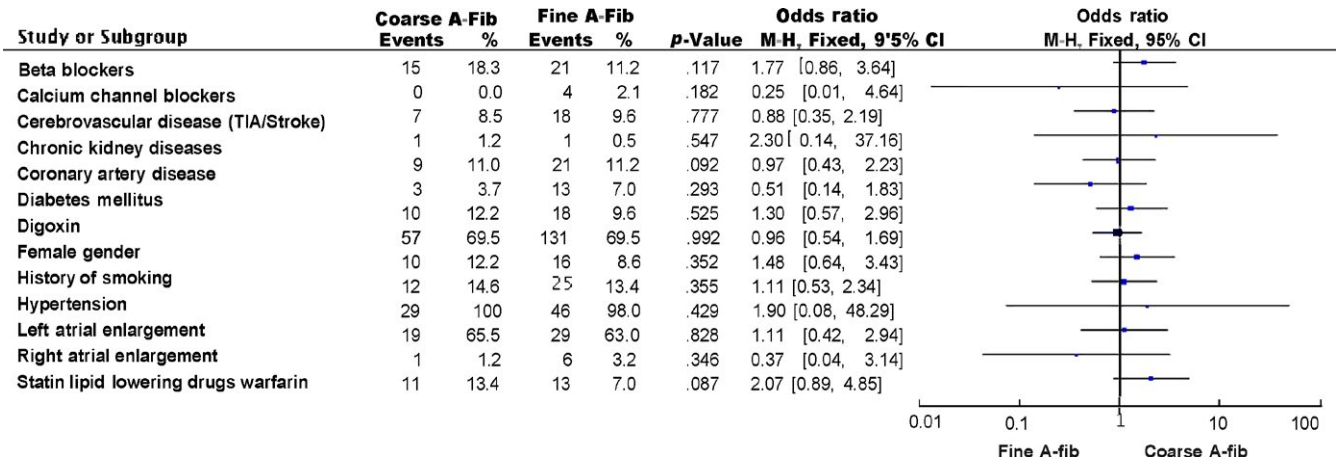


**FIGURE 2** Forest plot depicting the odds ration and 95% confidence interval of preexisting medical comorbidities comparing patients with coarse over those with fine atrial fibrillation

of the previous studies have focused on nonrheumatic AF patients exclusively. The main finding of this study is that in patients diagnosed with rheumatic MS, advanced age is associated with fine F wave in AF. In consistent with our findings, previous studies have indicated that there is a significant inverse correlation between F wave amplitude and age.(Yilmaz et al., 2007) Moreover, several studies have proposed that patients with FAF are older in comparison with those with CAF; and proportionally more elderly patients (age

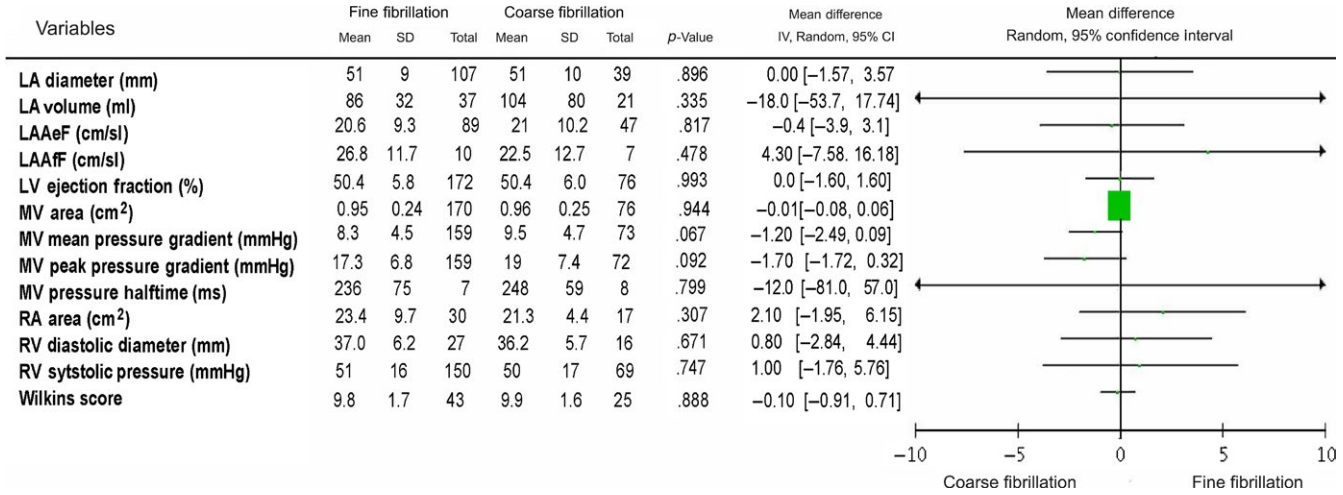


**FIGURE 3** Forest plot depicting the mean difference and 95% confidence interval of numerical echocardiographic measurements comparing patients with coarse to fine atrial fibrillation

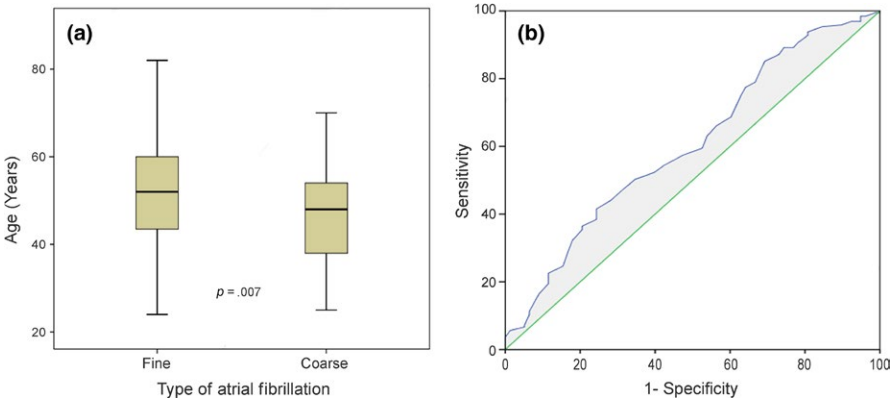


**FIGURE 4** The difference in age and the predictive role of age in determining the occurrence of fine F wave atrial fibrillation. The panel on the left depicts the boxplot of patient comparing the age in between the two groups and the Receiver Operator Characteristic plot is shown on the right where the positive part of the area under the curve is shaded

over 70 years) tend to present with FAF group.(Nault et al., 2009; Nobuyoshi et al., 2009).

However, in some studies, age is not shown to be significantly different between fine and coarse morphology groups (Morganroth et al., 1979; Selcuk et al., 2007) and no apparent effect of age on F wave amplitude has been observed despite an inverse impact on F wave frequency.(Xi, Sahakian, Frohlich, Ng, & Swiryn, 2004) Atrial remodeling and fibrosis have been demonstrated as factors affecting F wave size, which may clarify the role of aging on reducing the amplitude F wave in prolonged duration of AF.

According to our investigation similar percentage of patients in both the fine and CAF groups have been diagnosed with hypertension, diabetes mellitus, and chronic kidney diseases as well as smoking habits; which has been confirmed by the previous studies. (Morganroth et al., 1979; Nault et al., 2009) However, contradictory to our findings, Yilmaz et al. reported higher prevalence of hypertension and smoking among patients with FAF compared to CAF group (Yilmaz et al., 2007), while we have found only a trend for higher prevalence of coronary artery disease in patients with FAF.

Furthermore, this study has indicated that other clinical and echocardiographic variables do not differ between the fine and the coarse subtypes of AF. We report no significant difference in the nature and frequency of medication use between two groups of AF morphology. In fact, patients with AF are more likely to be treated with digoxin, beta blockers and warfarin anticoagulant irrespective of the amplitude of the F wave on ECG. Moreover, the current guidelines for administration of anticoagulation do not differ according to variations in F wave morphology among AF patients.(Nault et al., 2009; Selcuk et al., 2007) Interestingly, fibrillatory wave amplitude was not a predictor of successful cardioversion with vernakalant in patients with recent onset AF. (Mochalina et al., 2015).

Regarding echocardiographic findings that may alter the underlying pathophysiology for development of either F wave patterns in patients with AF, there has been controversy between different studies. The progressive enlargement of LA size may produce atrial contractile dysfunction by increasing wall stress and decrease compliance. However, several studies have failed to establish any relation between the diameters of LA and LV and its ejection fraction and the amplitude of the F waves in patients with AF.(Morganroth et al., 1979; Nault et al., 2009) Comparably, the transthoracic echocardiographic findings of the study by Mutlu et al., have illustrated no difference in the LA size, LV ejection fraction, peak transmitral

gradient, and mean transmitral gradient between patients with fine and CAF(Mutlu et al., 2003). This has been considered to produce the coarseness of AF(Li, Hwang, Tseng, Kuan, & Lien, 1995). Several reports have described increases in F wave amplitude with hypertrophy or enlargement of the LA size (Moss, 1984; Mutlu et al., 2003; Nakagawa et al., 2001; Selzer, 1960); a finding which is argued by several other investigators including the findings in current investigation (Blackshear et al., 1996; Josephson et al., 1977; Li et al., 1995; Morganroth et al., 1979; Nakagawa et al., 2001; Nault et al., 2009); where we failed to establish any difference in LA size between patients from either AF group.

Although our results showed a high prevalence of cerebrovascular disease in patients with AF as compared to those with sinus rhythm, we found no difference in history of cerebrovascular disease between fine and coarse morphologies of AF. Some published studies have evaluated the impact of F wave amplitude on thromboembolic risk in patients with AF and reported conflicting conclusions. It has been indicated that large atria are more likely to form and embolize blood clots than small atria(Moss, 1984). The reasoning behind the detailed examination in search of possible difference in echocardiographic finding comparing patients with coarse or fine AF related to the speculations regarding the presence of unorganized atrial contractions in CAF as opposed to a complete lack of atrial contraction in FAF. As the stagnation of the blood flow is an important factor that promotes clot formation, the presence of unorganized atrial contractions, on the other hand may increase the possibility of moving a preformed clot from the LA or LA appendage into the LV and systemic circulation. The absence of any association between LA size and F wave morphology in our study may explain the lack of correlation between thromboembolic events and F wave morphology. Blackshear et al. have failed to show association between F wave amplitude and thromboembolic risk.(Blackshear et al., 1996) However, these findings were in contrast with the result by Yilmaz et al., in which presence of CAF was found to be independently associated with 58.5% increase in the history of CVE ($p$ = .031). (Yilmaz et al., 2007) On the other hand, Nakagawa et al. showed increased thromboembolic risk in patients with FAF (Nakagawa et al., 2001). The majority of patients in these studies were elderly and had hypertension and other risk factors for thromboembolic events. Thus, high embolic outcomes in these studies cannot be clearly attributed to the F wave amplitude. Further prospective follow-up investigations may give more information in this regard.

Blackshear et al. in a study among 53 patients with nonrheumatic and seven patients with rheumatic AF, did not find an association between and LAA function in patients with nonrheumatic AF (Blackshear et al., 1996). They also found F wave amplitude not to be correlated with LAA velocity, LA size, increased LV mass, systolic dysfunction, or hypertension. These findings have been totally similar to our investigations. Other studies have drawn different conclusions. Li et al. reported that F wave size was related to LAA function in Asian people with nonrheumatic AF (Li et al., 1995). They found that in patients with coarse nonrheumatic AF, the LAA function was usually poor and the incidence rate of spontaneous echo contrast and LAA thrombus formation appeared to be higher in patients with CAF. However, Nakagawa et al. suggested that fine F wave was correlated with larger dysfunctional LAA and hypercoagulability (Nakagawa et al., 2001). Likewise, in the study conducted by Yamamoto et al. LAA flow velocity was reported to be significantly lower in patients with FAF (Yamamoto et al., 2005). In addition, a moderate inverse correlation between LAA flow velocity and mean fibrillatory rate has been reported before (Yilmaz et al., 2007; Yusuf et al., 2015).

This study was designed as cross-sectional study without a longitudinal follow-up; thus some limitations may exist. First, the variability in F wave size activity over time is not known. Second, the results might have potential bias due to single-center design; thus, the findings of our study might not be generalized. Reduced LV ejection fraction and valvular pathologies other than MS, that have a known association with the occurrence of AF, are not uncommon in patients with MS. As such we had to exclude a relatively large number of patients with MS who had concomitant cardiac pathologies. The strength of the current study has been its relatively large number of patients enrolled compared with previous studies. (Morganroth et al., 1979; Nault et al., 2009; Nobuyoshi et al., 2009; Selcuk et al., 2007).

In conclusion, we show that aging is an independent factor correlated with developing fine F wave among the patients with rheumatic MS, which may be a sign for advanced atrial remodeling. Of note, LA dimension/function were not different in patients with fine versus coarse morphology of AF. The other clinical and echocardiographic parameters do not differ between two morphology groups of AF patients.

## CONFLICT OF INTEREST

None.

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**How to cite this article:** Pourafkari L, Baghbani-Oskouei A, Aslanabadi N, et al. Fine versus coarse atrial fibrillation in rheumatic mitral stenosis: The impact of aging and the clinical significance. *Ann Noninvasive Electrocardiol*. 2018;23:e12540. https://doi.org/10.1111/anec.12540