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# TO STUDY QRS COMPLEX FRAGMENTATION IN RHEUMATOID ARTHRITIS

Medicine

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## ABSTRACT

**Introduction:** Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology affecting approximately 0.5–1% of the adult population worldwide. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Recently, there has been a lot of interest in QRS fragmentation as a screening tool in systemic diseases with Cardiac involvement.

**Aims and objectives:** 1. To study the prevalence of fragmented QRS complex in Rheumatoid Arthritis and it's correlation with demographic variables of Age, Sex and duration of disease. 2. To study correlation of fragmented QRS complex with RA factor and markers of inflammation, that is, ESR and CRP in rheumatoid arthritis. 3. To study correlation of fragmented QRS complex with echocardiographic findings in rheumatoid arthritis.

**Materials and Methods:** A cross-sectional study was undertaken at Rheumatology clinic in the department of Medicine at Hindu Rao Hospital, Delhi in 2017. Inclusion criteria for study group: 1. Patients satisfying 2010 revised ACR (American college of Rheumatology) and EULAR (European League Against Rheumatism) criteria for rheumatoid arthritis. 2. No cardiac symptoms or pre-existing heart disease or any abnormal findings on clinical cardiac examination .Exclusion criteria for study group:1.Uncooperative patients. 2. Patients with evidence of bundle branch blocks, wide QRS complex on ECG. 3. Patients detected to be diabetic, hypertensive or smoker. 4. Patients having cardiac symptoms or abnormalities on clinical cardiac auscultation. 5. Patients with other co-morbidities like morbid obesity, anemia, chronic kidney disease, liver disease.

**Statistical Methods:** All quantitative variables were presented in terms of range (minimum - maximum), mean ± standard deviation and median under each group separately. All the qualitative variables were presented in terms of frequency (percentage).Statistical significance of categorical variables was determined using chi square and Fisher's exact test. For test of significance between means, t-test and Z- test were applied where relevant. All statistical analysis was done using SPSS 24.0. Level of significance was taken as 0.05.

**Results:** There was significant correlation between presence of fQRS and high ESR in RA (p value 0.002). There was significant correlation between presence of fQRS and valvular involvement in RA (P value 0.002).There was significant correlation between presence of fQRS and diastolic dysfunction in RA (P value 0.002)

**Conclusion:** fQRS may be used to select patients with RA who can be further worked up by echocardiography to detect subclinical cardiac involvement and diastolic dysfunction.

## KEYWORDS

QRS complex, Rheumatoid arthritis, ECG.

## INTRODUCTION :

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology affecting approximately 0.5–1% of the adult population worldwide. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability[1]. Dysregulated immune system and a breakdown in self-tolerance result in chronic inflammation in joints and other organs. Because of its systemic nature, RA may affect a variety of organ systems,Cardiovascular involvement in RA is well recognized and is the most common cause of mortality in patients with RA[1-3]. Various cardiac manifestations of RA include pericarditis, cardiomyopathy/ myocarditis, cardiac amyloidosis, coronary vasculitis, arrythmia, valvular diseases, congestive heart failure and ischaemic heart disease[3]. The excess mortality in RA is not explained by traditional cardiac risk factors[4]. Das et al first defined fQRS as the QRS complexes with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary territory[5]. Fragmentation of QRS complex has been investigated as a predictor of myocardial fibrosis and scar, for prognostication in Ischemic heart disease and acute coronary syndromes and for predicting arrhythmias and conduction abnormalities. Recently, there has been a lot of interest in QRS fragmentation as a screening tool in systemic diseases with Cardiac involvement.

## AIMS AND OBJECTIVES:

1. To study the prevalence of fragmented QRS complex in Rheumatoid Arthritis and it's correlation with demographic variables of Age, Sex and duration of disease.
2. To study correlation of fragmented QRS complex with RA factor and markers of inflammation, that is, ESR and CRP in rheumatoid arthritis.
3. To study correlation of fragmented QRS complex with echocardiographic findings in rheumatoid arthritis.

## MATERIALS AND METHODS:

A cross-sectional study was undertaken at Rheumatology clinic in the department of Medicine at Hindu Rao Hospital, Delhi in 2017.

**Inclusion criteria for study group**: 1. Patients satisfying 2010 revised ACR (American college of Rheumatology) and EULAR (European League Against Rheumatism) criteria for rheumatoid arthritis. 2. No cardiac symptoms or pre-existing heart disease or any abnormal findings on clinical cardiac examination. In addition, 60 age and sex matched controls were recruited from Medicine Outpatient department from among the patients visiting the hospital for unrelated reasons. Controls were taken only to compare the prevalence of fQRS in Rheumatoid Arthritis with prevalence of fQRS in general population and hence only a standard 12 lead ECG was performed on the control subjects and the remainder of study was carried out only on the patients with rheumatoid arthritis. Rheumatoid Arthritis was defined as per 2010 ACR and EULAR classification criteria. Fragmentation of QRS complex was defined as presence of an additional R wave ®') or notching in the nadir of the S wave, or the presence of > 1 R' in 2 contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG. Patients with wide QRS complex or bundle branch blocks were excluded from the study.

**Exclusion criteria for study group:** 1. Uncooperative patients. 2. Patients with evidence of bundle branch blocks, wide QRS complex on ECG. 3. Patients detected to be diabetic, hypertensive or smoker. 4. Patients having cardiac symptoms or abnormalities on clinical cardiac auscultation. 5. Patients with other co-morbidities like morbid obesity, anemia, chronic kidney disease, liver disease.

**Inclusion criteria for control group:** 1. Age- and sex- matched controls were selected who had no joint pain, swelling, stiffness or any history of the treatment for the same. 2. No cardiac symptoms/pre-existing heart disease.

**Exclusion criteria for control group:** Same as that for the study group

**Study design:** An informed consent was taken from the patients fulfilling inclusion criteria and control subjects. A detailed history focusing on joint involvement, pattern, duration of disease and cardiac risk factors or any cardiac symptoms and treatment was taken. Detailed clinical examination was performed including Pulse, Blood Pressure, cardiac auscultation and focused examination to assess joint involvement was carried out. A standard 12 lead ECG with filter range 0.16–100 Hz, AC filter 60 Hz, paper speed 25 mm/s and 10 mm/mV was performed on all the participants. Controls were recruited only to compare the prevalence of fQRS in RA patients and in controls. Hence, only ECG was performed on controls and subsequent testing was restricted to patients with RA only. Qualitative testing for CRP and Rheumatoid factor was done on RA patients by immunotubidimetry technique. ESR was determined in RA patients only by Westergren's method. A standard 2D echocardiography with M-mode and Doppler was performed on RA patients only on a Philips Envisor-C machine with a 3-5 MHz transducer probe. Based on the presence of fragmented QRS complex, patients were divided in two groups- fQRS+ and fQRS-

**Statistical Methods:** All quantitative variables were presented in terms of range (minimum - maximum), mean ± standard deviation and median under each group separately. All the qualitative variables were presented in terms of frequency (percentage).

Statistical significance of categorical variables was determined using chi square and Fisher's exact test. For test of significance between means, t-test and Z- test were applied where relevant. All statistical analysis was done using SPSS 24.0. Level of significance was taken as 0.05.

**RESULTS:** The total number of 60 cases was studied along with a control group of 60 age- and sex-matched subjects. A total 46 of the 60 cases were females constituting 76.7%, and males constituted 23.3% of cases with a female preponderance of cases.

Age of the cases varied from 24 years to 68 years with a mean age of 46.67 years and a standard deviation of 11.980.Mean age of RA patients was 46.67 and mean age of control group was 46.03. P value for the difference between two means being 0.768 which was not significant. Sex composition of two groups was also the similar (P value 0.673). Hence cases and controls were comparable. In Cardiac examination findings of cases and controls Mean Pulse rate of RA cases was 79.83(per minute) with SD of 7.504 where as that of control group was 81.73 with SD of 7.37. Mean systolic Blood pressure in cases was 122.60 (mm of Hg) with SD of 8.786 and that of controls was 124.67 with SD of 7.041. Mean diastolic BP of cases was 78.50 (mm of Hg) with SD of 7.624 where as that of controls was 80.00 with SD of 7.235. There was no difference between cases or controls according to pulse rate, systolic blood pressure or diastolic blood pressure (P values 0.216, 0.435 and 0.329 respectively).Disease duration since diagnosis of cases ranged from 1 year to 30 years with a mean duration of 11.93 years and a standard deviation of 8.217. Median disease duration was 10 with IQR-13.

50 out of total 60 cases were positive for Rheumatoid factor and 10 were negative.

A total of 13 out of 60 RA cases showed the presence of fQRS on ECG giving a prevalence of 21.66 per 100 cases. In control group, 2 out of 60 subjects showed the presence of fQRS giving a prevalence of 3.33 per 100 cases.The fisher exact test statistic for the same analysis was 0.004329 which is statistically significant at $p<0.05$. Hence it can be said that cases with RA have a higher prevalence of fQRS positivity when compared to age- and sex-matched controls and this difference is statistically significant. Among female patients, 12 out of 46 (26.09%) were positive for fQRS whereas amongst male patients, 1 out of 14 (7.14%) patients had fQRS positive.

Fisher's exact test of proportion of fQRS positivity among males and females gave a p value of 0.264. Hence presence of fQRS has no statistically significant co-relation with sex of the patients.

Mean age of patients in fQRS positive group was 51.46 years and mean age in fQRS negative group was 45.340 years. Hence there was no statistically significant difference between mean age of patients in fQRS negative or positive groups (P value 0.122). There was no fQRS positive patient in age group of 21-30 years.

Mean disease duration in patients with fQRS positive was 11.923 years and mean disease duration in patients with fQRS negative was 11.936 years. P value for the difference was 0.996. Hence there was no statistically significant difference in the mean age of RA patient with fQRS positive and those with fQRS negative. (Table no -1)

**Table no. -1:** comparison of Age, Sex and disease duration between fQRS positive and fQRS negative RA patients.

| | fQRS Positive | fQRS Negative | P-value |
|---|---|---|---|
| Mean age (yrs) | 51.46 ( S.D.- 12.93) | 45.34 (S.D.-11.49) | 0.122 |
| Sex ratio | 12F:1M | 34F:13M | 0.264 |
| Mean disease duration (yrs) | 11.923 (S.D.- 9.142) | 11.936 (S.D.- 8.049) | 0.996 |

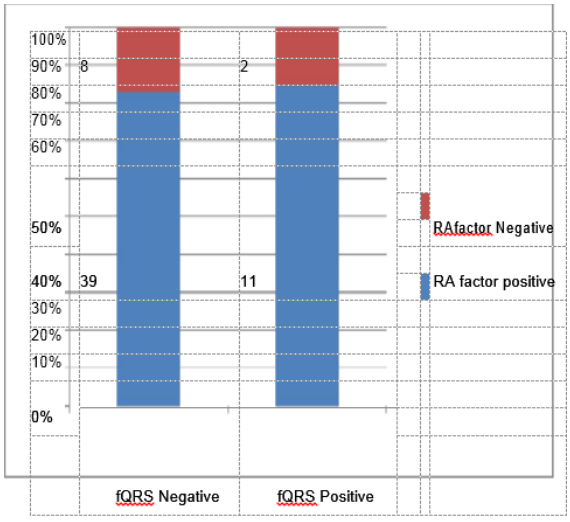


**Figure no.- 1: Component bar diagram showing correlation between fQRS and RA factor.**

Out of 47 cases who were fQRS negative, 39 were RA factor positive and among 13 fQRS negative patients, 11 were positive for RA factor.(Figure-1)

Chi- square analysis between fQRS Positive and fQRS negative groups gave a p-value of 0.889. Fisher's exact test gave a p-value of 1.00. Hence there is no statistically significant correlation between RA positivity and presence of fQRS. Out of 47 fQRS negative cases, 39 were positive for CRP and out of 13 fQRS positive cases, 12 were positive for CRP. Fisher's exact test gave a p-value of 0.668. Hence there is no statistically significant correlation between CRP and fQRS. Mean ESR among patients with fQRS positive was 41.462( Std dev- 11.392) where as mean ESR in fQRS negative group was 30.872 ( std dev- 8.274) .P-value for the difference was 0.002 which is highly significant. Hence, presence of fQRS among RA patients shows statistically significant correlation to elevated ESR. (Table-2)

**Table no. -2 comparison of fQRS positive and negative groups according to Rheumatoid factor and inflammatory markers.**

| | fQRS positive | fQRS negative | P-value |
|---|---|---|---|
| Rheumatoid factor(% of positive) | 84.61 | 82.97 | 1.00 |
| CRP( % of positive) | 92.30 | 82.97 | 0.668 |
| ESR (Mean) | 41.462 | 30.872 | 0.002 |
| | (S.D. -11.392) | (S.D.- 8.274 | |

**Table no. -3: Correlation of fQRS with Echocardiographic findings.**

| Echocardiographic findings | fQRS Positive (13 cases) | fQRS Negative (47 cases) | P value | Overall total in RA patients (60 cases) |
|---|---|---|---|---|
| Pericardial involvement | 3 (23.08%) | 4(8.51%) | 0.147 | 7 (11.66%) |
| Valvular involvement | 5(38.46%) | 3(6.38% | 0.002 | 8(13.33%) |
| Diastolic dysfunction | 10(76.92%) | 14(29.78%) | 0.002 | 24(40.0%) |

Overall pericardial involvement was seen in 7 of the 60 RA patients (11.66%).3 patients out of 13 fQRS positive patients had pericardial involvement on echocardiography (23.08%) where as 4 of the 47 (8.51%) fQRS negative patient had pericardial involvement.(Table-3) This difference however was not statistically significant (P-value - 0.147).Overall valvular defects(Table-4) were seen in 8out of 60 RA patients (13.33%).Valvular defects were seen in 5 of the 13 fQRS positive patients (38.46%) as compared to 3 of the 47 fQRS patients (6.38%). This difference between two groups was statistically significant with P- value= 0.002.

**Table no. -4: Valvular abnormalities in study group**

| Valvular abnormality | | | fQRS negative | fQRS positive | Total |
|---|---|---|---|---|---|
| | | | (47 cases) | (13 cases) | (60 cases) |
| Mitral Regurgitation | 0 | 2 | 2 | | |
| Tricuspid | | | 1 | 0 | 1 |
| regurgitation | | | | | |
| Aortic regurgitation | 1 | 0 | 1 | | |
| Combined | MR | plus | 0 | 2 | 2 |
| AR | | | | | |
| Combined | MR | plus | 1 | 1 | 2 |
| TR | | | | | |

Diastolic dysfunction was present in 10 of the 13 fQRS positive patients (76.92%) whereas only 14 of 47 fQRS negative patients (29.78%) had diastolic dysfunction. P value for chi-square test for the above analysis was 0.002 and hence there was statistically significant difference between proportion of patients with fQRS positive having diastolic dysfunction and proportion of patients with fQRS negative having diastolic dysfunction.None of the studied patients had significant systolic dysfunction.

Subgroup analysis between patients with some echocardiographic abnormality and no echocardiographic abnormality revealed, Out of total 60 cases, 28 patients had some or a combination of echocardiographic abnormalities and 32 patients had no echocardiographic abnormality. Out of 32 patients with normal echocardiograms, only 2 patients had fQRS positive where as 11 of 28 patients with some form of echocardiographic abnormality had fQRS positive. This difference was statistically significant (P value 0.004).

**DISCUSSION:**

Cardiovascular involvement in RA has always been a topic of active research with olden day autopsy studies reporting rheumatoid granulomas involving different structures within heart, fibrosis, valvulitis [6] to very high prevalence of pericardial involvement which was not detected clinically[6,7]. This was followed by an era of echocardigraphic studies reporting pericardial involvement, valvular defects, various degrees of diastolic dysfunction and cardiomyopathies[8-11, 12-14]. Conduction disturbances and arrhythmias in RA also got focused upon[15]. In the recent past, most focus has been on increased risk of atherosclerosis, myocardial infarctions, cerebrovascular diseases and congestive heart failure in RA [16].

Fragmentation of QRS complex on ECG was first formally defined by Das et al[5] in 2006 and since then this easily evaluable parameter has been studied as a marker of old MI, fibrosis, scar; as a prognostic marker in myocardial infarctions and as a predictor of need for further cardiac interventions [17-20]. Other investigators studied its significance in cardiomyopathies where as other groups studied risk of arrhythmias that could be predicted by this tool in various conditions [21]. fQRS was studied in sarcoidosis, systemic sclerosis, SLE, behcet's syndrome and ankylosing spondylitis [22]

Then in 2012, a study by Kadi et al [23] reported higher prevalence of fQRS in RA as compared to controls and association of fQRS with disease duration in a pilot study.

However our study was designed differently from the one conducted by Kadi et al in the way that Kadi et al performed a baseline TMT and echocardiographic examination on all subjects and excluded subjects with abnormalities on echocardiography or TMT from the study. When we compared the prevalence of fQRS between cases and controls, prevalence of fQRS in cases was 21.66% (13 of 60 cases) and prevalence of fQRS in controls was 3.33% ( 2 of 60 controls). P-value for the comparison was 0.004. Hence Prevalence of fQRS was significantly higher in cases of RA compared to healthy age- and sex-matched controls. Previous study by Kadi et al[23] had reported fQRS prevalence in RA of 37.5% and in controls as 5.7%.

Kadi et al reported a positive association between fQRS and disease duration in their study. They reported median disease duration amongst fQRS positive patients as 10(IQR8) and that amongst fQRS negative cases as 5 (IQR 2). Where as in our study, median disease duration in fQRS positive group was 8 (IQR 15) and it was 10(IQR 14) in fQRS negative group. There was a wider distribution of data in disease duration in our study as we included all the consecutive patients with varied durations of disease.

Kroot et al studied an inception cohort of 622 patients with RA and suggested that the mortality in first 10 years of the disease was not different from the general population[24]- implying that reported increase in cardiovascular mortality occurs after the first 10 years of the disease process. Whereas Meredith et al reported no correlation between cardiovascular deaths and disease duration of RA [25]. Similarly Meune et al conducted a systemic review of 17 cohort studies with a total of 91,916 patients and found that Standardized mortality ratio had no correlation with disease duration (P value 0.513) [26].

Similarly there was no significant difference between two groups when compared for rheumatoid factor (P value- 1.00).We did not find any significant difference between groups in terms of CRP positivity either (P value-0.668).

However ESR of the fQRS positive and fQRS negative groups differed significantly (Mean ESR 41.46 vs 30.872, P value- 0.000). This discordance of inflammatory markers in this case could be due to the reason that because of limitation of resources, we had utilized qualitative estimation of CRP instead of high sensitivity quantitative CRP assays so the information given by CRP testing was limited. This correlation with inflammatory markers was particularly interesting because ESR and CRP have been used as tools for assessing disease activity status in RA and atherosclerosis has now been established as resulting from chronic inflammation with hs-CRP being projected as an independent risk factor of cardiac disease [27].Cetin et al [28] also reported independent association of fQRS with systemic inflammation in patients with acute coronary syndrome. Meredith et al in their study also reported an increased risk of death from cardiovascular events in patients of RA with more than or equal to 3 recorded ESR of 60mm at the end of first hour or higher (Hazard rate 2.03, 95% CI 1.45-2.83) [29]. Similarly Wallberg et al in their retrospective cohort study found that a high last registered ESR before cardiovascular event added to the mortality in RA patients [30]. As our study also found an association between fQRS and elevated ESR, it could be likely that fQRS in RA patients is also associated with inflammation and could also be related to the severity of the disease. Further longitudinal studies will be required to assess this point and also to evaluate impact of therapy of RA on fQRS with remission of disease.

Overall analysis of all the patients with RA showed that 11.66 % had pericardial involvement which is comparable with previously reported rates by Guedes et al[31]. 23.08 % of fQRS positive patient had pericardial involvement as compared to 8.51% of fQRS negative patients. However this difference is not significant (P-value 0.147).

Overall 13.33% of patients with RA had valvular defects. Nimchinov EN et al[32] had reported valvular defects in 7.9% of RA patient and Guedes et al[31] reported a very high rate of valvular involvement with mitral regurgitation being seen in upto 80% but they utilized trans-esophageal echocardiography for their study. In the fQRS positive group, 38.46% patients had valvular defects (5 patients) but in fQRS negative group only 6.38% had valvular involvement (3 patients). This was a significant difference (P value 0.002), implying that fQRS in RA patients is associated with presence of valvular defects.

Overall 40.00% of RA patients had some degree of diastolic dysfunction. This is similar to the reported rate by Udayakumar et al from Chennai who found diastolic dysfunction in 42.2% of RA patients [14]. We found a significant difference in proportion of patients with diastolic dysfunction between the two groups with 76.92% of fQRS positive patients(10 of 13 patients) having diastolic dysfunction as compared with 29.78% of those in fQRS negative (14 of 47 patients) group. Positive predictive value of fQRS for diastolic dysfunction was 76.92% and Negative predictive value was 70.21%. Hence even

though fQRS may not be an appropriate tool to rule out subclinical diastolic dysfunction in RA because of poor sensitivity, its presence is highly significant and should lead to further evaluation of patients by Doppler echocardiography.

## CONCLUSIONS:

There was significant correlation between presence of fQRS and high ESR in RA P value 0.002).There was significant correlation between presence of fQRS and valvular involvement in RA (P value 0.002). There was significant correlation between presence of fQRS and diastolic dysfunction in RA (P value 0.002).

## Recommendations:

Better control of disease activity may decrease incidence of cardiac disease in RA. fQRS may be used to select patients with RA who can be further worked up by echocardiography to detect subclinical cardiac involvement and diastolic dysfunction.

## Limitations:

As ours was a cross-sectional study, the prognostic significance of fQRS in RA could not be assessed, further longitudinal studies can be conducted to assess the prognostic significance of fQRS in RA.

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