Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

Fragmented QRS — Its significance

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ARTICLE INFO

ABSTRACT

Fragment QRS (fQRS) complex is a myocardial conduction abnormality that indicates myocardial scar. It is defined as additional notches in the QRS complex. Though initially fQRS was defined in the setting of normal QRS duration (<120 m s), later it has been expanded to include conditions with wide QRS complexes as in bundle branch block, ventricular ectopy and paced rhythm, when more than 2 notches are present. It is an important, yet often overlooked marker of mortality and arrhythmic events in many cardiac diseases. The significance of fQRS lies in the fact that it just requires a surface ECG for its recording and the value of information about the condition of the heart it dispenses based on the clinical setting. We review the role of fQRS in predicting adverse cardiac events in various conditions.

1. Introduction

Appearance of additional spikes in the QRS complexes has gained interest in recent years. These are different from the standard rSR′ pattern seen in right bundle branch block (RBBB) and the notched R waves seen in left bundle branch block (LBBB) [1]. Fragmented QRS (fQRS) was initially defined as additional spikes in the QRS complex in the absence of bundle branch block [2]. But later the definition was widened to include additional notches over and above the pre-existent pattern even in wide QRS due to bundle branch block, paced rhythm or ventricular ectopy. This is termed fragmented wide QRS (f-wQRS) in contrast with fragmented narrow QRS (QRS duration <120 m s). fQRS in a paced rhythm has been designated f-pQRS [3].

Over the past few years, literature on fQRS has evolved, with studies in a wide variety of cardiac conditions ranging from coronary artery disease (CAD), cardiomyopathies, valvular heart disease, aortic dissection, pulmonary embolism, congenital heart disease and cardiac channelopathies. Studies of fQRS in various primarily non-cardiac conditions like obstructive sleep apnea, renal disease, cirrhosis of the liver, radiotherapy in breast cancer,

autoimmune disorders and beta thalassemia have also been published. This review is an attempt to compile clinically relevant information from the available literature, focusing primarily on cardiac conditions.

2. Definition

fQRS can be defined as the presence of additional R′ waves or a notch in the nadir of the R or S wave (fragmentation) in two contiguous leads corresponding to a coronary territory in a routine 12-lead ECG (0.5—150 Hz) [4]. Fragmented wide QRS (f-wQRS) is defined as two or more notches in the R or S wave, in two contiguous leads corresponding to a coronary territory (anterior, lateral or inferior) (Fig. 1). The notches should be separated by at least 40 m s.

3. Inter and intra-observer variability

Inter and intra observer variability of fQRS has been studied by Vandenberk B et al. [5]. Hundred ECGs with fQRS were evaluated by two experienced and 3 novel observers. Fleiss and Cohen's Kappa was calculated among subgroups. There was a significant inter-observer variability with a Kappa of 0.651. Experienced observers had a better agreement with a Kappa of 0.823. Inter-observer variability was much higher in paced-rhythm (f-pQRS) compared with normal rhythm, with Kappa 0.493 vs 0.664 (p < 0.001). Intra-observer variability had a Kappa between 0.736 and 0.880. So visual assessment variability will depend on experience as well as the

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underlying rhythm.

4. Automation of detection

Conventionally fQRS assessment is done by visual inspection of the 12 lead ECG by trained operators. Automation of detection by computer-based algorithms have been attempted [6]. Out of 40 ECGs randomly selected from a database, 31 were opined to be suitable for analysis by two experienced cardiologists. They demonstrated a sensitivity of 0.897 and specificity 0.899 for the detection of f-QRS by their algorithm. Authors went on to suggest that automation will speed up the detection and reduce human error as well as allow implementation of hospital-based remote monitoring. This could also be an option in implantable cardioverter defibrillator devices (ICD) in future.

5. Coronary artery disease

5.1. Prognostic significance of inferior vs. anterior lead fQRS

Though the correlation of fQRS with various adverse cardiac events has been widely studied, a little was reported comparing the outcomes of fQRS on inferior vs anterior leads. Eyuboglu et al. have studied the severity of CAD in patients with inferior and anterior lead fQRS. Anterior lead fQRS was associated with higher incidence of multivessel disease (p = 0.007) and greater severity of CAD, as indicated by a higher median SYNTAX score (p = 0.047) [7]. Terho HK et al., evaluated the prognostic significance of fQRS on inferior, anterior and lateral leads. fQRS was common in inferior leads. Mere presence of fQRS without an established cardiac disease didn't predict an adverse cardiac outcome. Lateral lead fQRS had the least incidence among the three but carried a higher risk of all-cause mortality (p = 0.001) [8].

5.2. fQRS: a marker of myocardial scar

The significance of fQRS was initially studied and compared with Q wave in patients undergoing nuclear stress test [2]. The sensitivity, specificity, and the negative predictive value for myocardial scar as were 36.3%, 99.2%, and 70.8%, respectively, for the Q wave alone; 85.6%, 89%, and 92.7%, respectively, for the fQRS; and 91.4%, 89%, and 94.2%, respectively, for the Q wave and/or fQRS. Therefore, fQRS on a 12-lead ECG is a marker of a prior MI, with a substantially higher sensitivity and negative predictive value compared with the Q wave.

Several studies have evaluated the significance of fQRS in conditions like ST elevation [9] and non ST elevation myocardial infarction [10], stable angina pectoris [11], relationship with percutaneous coronary intervention (PCI) [12], cardiac rehabilitation [13], collateral circulation [14], slow flow [15], coronary ectasia [16] left ventricular thrombus [17] and aneurysm [18].

5.3. ST elevation myocardial infarction (STEMI)

fQRS can be used as a tool for risk stratification in STEMI. Tanriverdi et al. studied the association of fQRS with in-hospital mortality rate in STEMI patients. Patients (n = 248) with fQRS on ECG taken within 48 h had higher incidence of in-hospital mortality (p = 0.002). Greater the number of leads with fQRS, higher was the in-hospital mortality rate (p = 0.023) [19]. The prognostic value was better if fQRS was combined with distorted QRS to predict in-hospital mortality rate (p < 0.001) [19].

fQRS seen on admission is often indicative of previous myocardial scar and is associated with increased morbidity and mortality. The relationship between fQRS before and after primary PCI has been assessed by Kocaman SA et al. [20]. Patients with fQRS on admission had higher levels of cardiac troponin, longer pain to balloon time, higher Killip score, higher QRS duration and more frequent Q waves, compared with those without fQRS (P ranging from 0.004 to <0.001). They usually had wider jeopardized myocardium (p < 0.001), in the left anterior descending coronary artery territory. Absence of fQRS on admission predicted more ST resolution, better myocardial reperfusion and reduction in QRS duration.

Many studies on the usefulness of fQRS in predicting the outcomes of STEMI after PCI were published. Akgul et al. [21] published a prospective study comparing the one year outcomes of patients who underwent PCI for STEMI with fQRS and without fQRS. The STEMI with fQRS group had higher all-cause mortality (p < 0.001). fQRS is shown to be a significant independent predictor of one year all-cause mortality (p = 0.001) [21]. STEMI patients with fQRS had higher incidence of in-hospital mortality (p = 0.009) and contrast induced nephropathy (p = 0.029) after undergoing PCI [22]. In a retrospective study, patients with fQRS accompanying STEMI experienced higher rates of cardiovascular mortality (p = 0.028) as well as all - cause mortality (p = 0.022). In addition, it was also established that presence of fQRS was associated with lower left ventricular ejection fraction (LVEF) and higher risk of heart failure (p < 0.001) [23]. Higher cardiac biomarker levels, lower STEMI resolution rate and lower LVEF after PCI were noted among patients
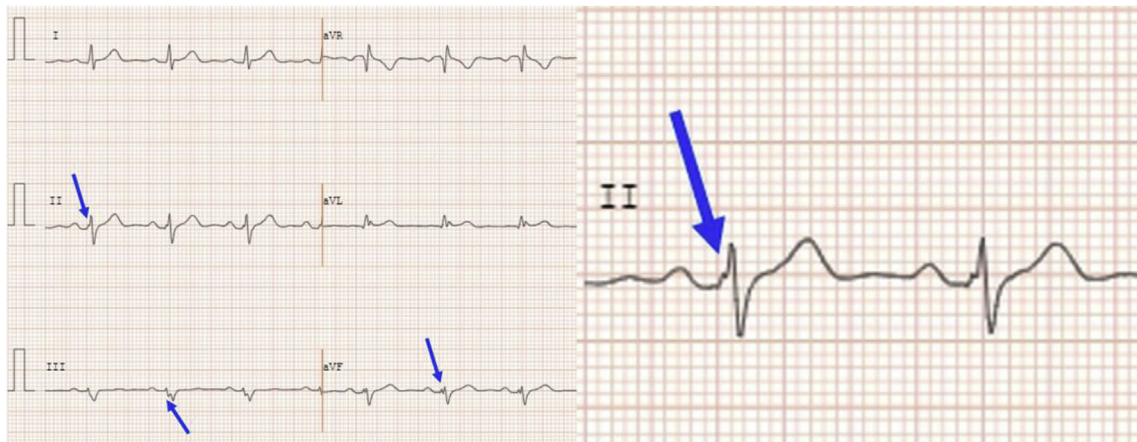

Fig. 1. Fragmented QRS in inferior leads.

with fQRS (p < 0.01) [24]. Kanjanahattakij N., et al. conducted a meta-analysis of six studies that compared mortality rates among STEMI with fQRS and without fQRS groups who underwent PCI, which showed that the presence of fQRS increased the mortality up to 3 times compared to the absence of fQRS [25]. The combined use of fQRS and neutrophil:lymphocyte ratio (NLR) for predicting the in-hospital mortality rate of STEMI patients after PCI was suggested by Tanriverdi et al. It was ratified that NLR ≥5.47 had higher incidence of fQRS (p = 0.001). NLR above the cut off value and fQRS had significant association with higher in-hospital mortality rate (p < 0.001) [26].

fQRS as a manifestation of local conduction abnormalities in the ventricular myocardium and scar tissue has been established time and again. However, its association with atrial conduction abnormalities like atrial fibrillation (AF) in the setting of STEMI is the subject of interest currently. 171 STEMI patients who underwent PCI were studied for new onset AF after revascularization. It was discerned that fQRS with STEMI is associated with higher rates of new onset AF (p = 0.001) [27]. More number of studies with larger sample size are required to vouch for the association.

The success of a cardiac rehabilitation (CR) programme has traditionally been gauged by the quality of life, incidence of reinfarction and mortality rate. Bulut et al. studied 160 patients admitted with STEMI and fQRS who were divided into two groups based on their participation in exercise based CR programme. It was affirmed that the exercisers group had lesser rate of persistent fQRS after CR marking the electrical stabilisation of infarcted myocardium (p = 0.034) [13]. This study might open up newer territories in the assessment of a successful CR programme based on the persistence or disappearance of fQRS on serial ECGs.

5.4. Non-ST elevation myocardial infarction (NSTEMI)

fQRS is conducive in identifying the involved vessel in NSTEMI. In a retrospective study of 183 patients admitted for NSTEMI, fQRS in respective leads had 77.1% sensitivity and 71.5% specificity in identifying the culprit vessel [10]. The usefulness of fQRS in differentiating NSTEMI from unstable angina (UA) was studied by Lang D et al. Incidence of fQRS was higher among the NSTEMI group than the UA group (p = 0.047) [28]. Adverse cardiac events like recurrent angina, recurrent MI, heart failure etc., were higher among the NSTEMI with fQRS group (p = 0.028) [29]. In a study by Bozbeyoglu E et al., out of 433 NSTEMI patients were divided into fQRS (85) and non-fQRS groups (348). In-hospital, 30 − day and 12 month mortality rates of two groups were compared. It was found that there was no significant difference in the in-hospital and 30-day mortality rates but 12 month mortality rate was higher in the fQRS group, 15.2% as compared to 5.4% in non-fQRS group (p = 0.006) [30].

5.5. Collateral circulation in chronic total occlusion (CTO)

The value of fQRS in determining poor collateral coronary circulation in patients with chronic stable angina was studied by Bonakdar H et al. Seventy nine patients with stable angina were evaluated by single photon emission computed tomography (SPECT) for myocardial scar. Coronary angiogram was also performed for CTO of coronary vessels besides understanding the status of collateralisation. fQRS was more frequent in patients with poor collaterals (p < 0.001). SPECT showed significantly higher summed stress score and summed rest score in the patients with poor collateralisation and hence in the positive fQRS group (p < 0.001) [14].

5.6. Coronary slow flow (CSF)

Slow flow of blood through the distal coronary branches in the absence of occlusion is thought to be due to endothelial dysfunction, atherosclerosis, microvascular vasomotor dysfunction and increased platelet aggregability. This can be associated with angina, myocardial ischemia, acute myocardial infarction (AMI). In a study by Yilmaz et al., 60 patients with CSF and 44 patients with normal coronaries were studied. The incidence of fQRS was shown to be higher among the CSF group as compared to the patients with normal coronaries (p = 0.005) [31]. In another study by Cakmak et al., 165 patients were studied, of which 112 patients showed CSF and the rest were controls. It was established that incidence of CSF was higher in the fQRS group than non-fQRS group (p < 0.001). Multivariate analysis showed that fQRS is a reliable marker of CSF (p = 0.03) [15].

5.7. Left ventricular thrombus

Left ventricular thrombus formation is a known complication of AMI and is associated with poor post-PCI outcomes in patients with AMI. The risk factors for left ventricular thrombus formation in the setting of AMI include large infarct size, anterior wall myocardial infarction, apical wall motion abnormality and low ejection fraction. fQRS has been suggested as an ECG marker for left ventricular thrombus formation. In a prospective study of 148 patients admitted for AMI, 53.1% of the patients with left ventricular thrombus had fQRS in leads V4−V6 (p < 0.001) and 75% of these patients had unsuccessful PCI (p = 0.002) [17]. This study projected the significance of fQRS in predicting the risk of left ventricular thrombus in patients with AMI.

5.8. Left ventricular aneurysm

Left ventricular aneurysm is an important long term complication of myocardial infarction and occurs in 3.5−9.4% of cases. fQRS in left sided leads in the absence of LBBB has been associated with left ventricular aneurysm [18]. ECG recordings of patients with left ventricular aneurysm were compared with those of patients without left ventricular aneurysm (with and without CAD). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of fQRS in predicting left ventricular aneurysm were 50%, 94.6%, 83.3% and 79.2% respectively.

6. Dilated cardiomyopathy (DCM)

DCM is associated with ECG changes that mark left atrial enlargement, LBBB and sometimes left ventricular hypertrophy. Studies showed that fQRS in non-ischemic DCM was found to be associated with left ventricular dyssynchrony. Tigen K et al., established that the maximal difference in time to attain peak systolic velocity (PSV) between any two myocardial segments and maximal difference between PSV and mean systolic velocity of all segments were significantly high in fQRS group (p = 0.001 and p = 0.003 respectively). This was suggestive of significant intraventricular dyssynchrony in fQRS positive patients with narrow QRS and sinus rhythm [32]. Another prospective study by Zhao L et al., observed that fQRS in idiopathic DCM patients with narrow QRS complex was confederated with left ventricular dyssynchrony as indicated by the time lapse between peak anteroseptal wall and posterior wall strain >130 msec or longitudinal strain delay index >25% (p < 0.001). On follow up after two years, the left ventricular dyssynchrony worsened in the fQRS group (p < 0.05) [33].

7. Role of fQRS in heart failure

The value of fQRS in predicting the mortality of patients with heart failure has been established in numerous studies. A recent meta-analysis that included 5180 patients with heart failure with reduced ejection fraction (HFrEF) established the association of baseline fQRS with increased mortality (risk ratio = 1.49, 95% confidence interval: 1.19–1.86, p = 0.001) [34]. In another study, fQRS in ≥3 leads was identified as an independent predictor of mortality in patients with HFrEF [35]. However, conflicting results were published by two studies vis-à-vis, the value of fQRS in the setting of heart failure with preserved ejection fraction (HFpEF). In a prospective study that included 239 patients admitted with left ventricular diastolic dysfunction, fQRS group had higher incidence of heart failure, higher levels of BNP and hs-TNT than non-fQRS group (p < 0.001, p = 0.001 and p = 0.007 respectively) [36]. Contrarily, in a retrospective study that included 100 patients with asymptomatic left ventricular diastolic dysfunction, no difference was noted in the proportion of patients with fQRS among those who developed HFpEF and those who remained asymptomatic on follow up (p = 0.78) [37].

Currently, cardiac resynchronisation therapy (CRT) is limited to the patients with wide QRS complex (>149 msec) and LBBB pattern. However, various studies demonstrated that 27–52% of the patients with HFrEF have narrow QRS complex (<150 msec) [38,39]. Studies have also shown that 20–50% of the patients with HFrEF and narrow QRS complex have left ventricular dyssynchrony [40,41]. These results demonstrates that a significant number of patients with left ventricular dyssynchrony may be deprived of CRT, as per the current guidelines. On the flip side, echocardiography based studies on application of CRT in HFrEF patients with narrow QRS complex have failed to demonstrate any benefit with CRT in the patient outcome [42,43]. As it was discussed in the previous section, fQRS is a marker of left ventricular dyssynchrony in HFrEF patients with narrow QRS complex on the ECG. This association can be considered in future studies on expanding the scope of CRT to these patients.

Response to CRT is being assessed traditionally by NYHA functional class, 6 min walk test, quality of life questionnaires, left ventricular volumes and LVEF [44]. Resolution of fQRS was ratified as a marker of response to CRT after a follow up of 6 months, in a prospective study. 58% of the patients showed >14% reduction in LV end systolic volume (LVESV) and number of leads with fQRS decreased from 4.4 ± 1.8 to 1.7 ± 1.6 in patients who responded to CRT (p = 0.001 and p < 0.001 respectively) [45]. If further studies show similar results, fQRS resolution might assume a key role in the assessment of CRT response.

8. fQRS in left ventricular noncompaction cardiomyopathy

Left ventricular noncompaction cardiomyopathy (NCM) is a rare genetic disorder characterised by multiple trabeculations in the left ventricular myocardium that arises due to noncompaction of embryonic mesh-like myocardial fibre network [46,47]. NCM results in various complications like left ventricular systolic dysfunction, ventricular arrhythmias and systemic emboli [46]. Murphy RT et al., studied 45 patients admitted for NCM, of which, 91% showed abnormal ECG. LBBB, pathological Q waves, poor R wave progression, ST segment variations and T wave inversion were the abnormalities noted [46]. fQRS was noted in 48% of the patients with NCM in a study by Ning XH et al. It was also demonstrated that fQRS group had higher mortality rate when compared with the non-fQRS group of NCM patients (p = 0.005). Narrow fQRS was noted as an independent predictor of all-cause-mortality in these patients (Hazard ratio, HR = 5.33 and p = 0.045) [48]. In another study, fQRS

in the setting of NCM was established as an independent predictor of arrhythmias and cardiovascular mortality (HR = 3.850, 95% CI 1.062 to 9.947, p = 0.002 and HR = 2.719, 95% CI 1.494 to 9.262, p = 0.005 respectively) [49]. These studies assert the usefulness of fQRS in stratifying the risk of mortality and arrhythmic events in NCM patients.

9. Takotsubo cardiomyopathy

In a study of 33 Takotsubo cardiomyopathy (TTC) patients, the incidence of J wave and/or fQRS on ECG was 29% and these patients were categorised as group A. The rest were categorised as group B. On comparing the LVEF of group A with that of group B, it was noted that the group A had lower values. It was also identified that the group A had a higher summed defect score of single-photon emission computed tomography and creatine kinase MB isoenzyme (CKMB). The J wave was a significant marker of sudden cardiac death and ventricular arrhythmias in these patients (p = 0.026) [50]. However, there are no direct studies on correlation of fQRS with adverse cardiac events in the setting of TTC.

10. Hypertrophic cardiomyopathy

Various studies demonstrated the role of fQRS in predicting ventricular arrhythmias in the setting of HCM. In a prospective study of 167 HCM patients, ventricular arrhythmias and sudden cardiac death were considered as the major arrhythmic events. The study established that fQRS is significantly associated with ventricular arrhythmias and major arrhythmic events (unadjusted HR = 6.17, 95% CI 2.46–15.49, p < 0.001 and unadjusted HR 5.12, 95% CI 1.38–19.01, p = 0.014 respectively). fQRS was also identified to be an independent predictor of VA and major arrhythmic events in HCM (adjusted HR 6.28, 95% CI 2.49–15.84, p < 0.001 and adjusted HR 6.04, 95% CI 1.49–24.39, p = 0.011 respectively) [51].

As mentioned in the previous sections, fQRS is a marker of myocardial scar. Ratheendran AC et al. compared ECG abnormalities with Gadolinium enhancement on cardiac MRI (CMR) to predict myocardial scar in patients with HCM. Out of 39 HCM patients, 23 demonstrated fQRS on ECG (63.89%). When all the patients were subjected to Gadolinium enhanced CMR, fQRS group showed higher incidence of late Gadolinium enhancement, that indicated myocardial scar, when compared with non-fQRS group (fQRS group - 84.61%, non-fQRS group - 10%, p < 0.001). Sensitivity, specificity, positive predictive value and negative predictive value of fQRS in predicting myocardial scar were 84.6, 90.0, 95.6 and 69.2% respectively [52].

11. Brugada syndrome

Association of fQRS with Brugada syndrome [53] and its role in predicting adverse events in these patients have been explained in various studies. In a study of 115 BS patients, fQRS was noted in 43% of them. Thirteen patients suffered VF of which, 11 patients (85%) demonstrated fQRS. 50% of the patients who suffered syncope and 34% of the asymptomatic patients also showed fQRS (p value of all adverse events <0.01) [54]. In a meta-analysis by Meng L et al., it was found that unadjusted RR of VF in the presence of fQRS in Brugada syndrome is 4.23 (95% CI 1.68 to 10.61, p = 0.002) based on five studies by Refs. [54–58]. Adjusted HR of sudden cardiac death in Brugada syndrome was found to be 3.61 (95% CI 2.11 to 6.18, p < 0.00001) as demonstrated in three studies [59–62].

12. Arrhythmogenic right ventricular dysplasia (ARVD)

Role of fQRS in foreboding the prognosis of ARVD was described

in a few studies. fQRS was noted in 59% of 78 patients studied prospectively by Canpolat U et al., During 38 ± 14 months follow up, 50% of the total patients suffered adverse cardiac events in the form of sudden cardiac death or ventricular arrhythmias. fQRS was significantly associated with arrhythmic events (p < 0.001). Number of leads with fQRS was higher in the fQRS group with greater risk of arrhythmias (fQRS group - 5.08 ± 2.5 vs non-fQRS group - 1.14 ± 1.7 and p < 0.001) [63]. In another study that included 30 ARVD patients, surface ECG abnormalities were compared with corresponding abnormalities on endocardial and epicardial electroanatomic mapping. Twenty five (83%) patients had fQRS in two or more contiguous leads. Endocardial very low bipolar voltage area was larger in fQRS group than in non-fQRS group (median 19 cm^2 vs median 5 cm^2; p = 0.02). Epicardial late potential percentage (median 24% vs median 8%; p = 0.002) was also significantly larger in fQRS group. These results established fQRS on surface ECG as an indicator of larger voltage substrate abnormalities on electroanatomic mapping in the setting of ARVD [64].

13. Idiopathic ventricular fibrillation

Patients with idiopathic ventricular fibrillation (IVF) commonly succumb to sudden cardiac death. A few suffer ventricular fibrillation (VF) following physical or mental exertion. Studies showed that J point elevation and fQRS on resting ECG are risk indicators of IVF. In a retrospective study of 171 patients who survived cardiac arrest due to VF or syncope due to self-terminating VF. They were divided into three groups based on the presence of fQRS and J wave (group 1), J wave alone (group 2) and normal ECG (group 3). It was established that the incidence of syncope, cardiac arrest and VF episodes, as recorded by implantable cardioverter defibrillator (ICD) or pacemaker, was highest in group 3 followed by group 2 and group 1 (13.4 ± 5.6/year - group 1, 10.8 ± 3.9/year - group 2 and 9.8 ± 4.2/year - group 3) (HR = 3.2; 95% CI, 1.1–7.9; p = 0.01) [65].

14. Conclusion

The value of fQRS in cardiology is much higher than what is being understood currently. The application of fQRS in various clinical settings has been expanding as new studies kept demonstrating its significance. Our article attempted to summarise various studies available on the significance of fQRS in a few important clinical scenarios in the field of cardiology. However, its role has been demonstrated in many non-cardiac diseases, the discussion of which is beyond the scope of this article. Clinical practitioners should heed to fQRS on ECG and investigate the patient for an underlying cardiac disease depending on the clinical context.

Declaration of competing interest

We have no conflicts of interest to declare regarding our manuscript: "Fragmented QRS – Its Significance".

Acknowledgement

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