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REVIEW ARTICLE

QRS fragmentation: its role in sherlocking the arrhythmogenic heart

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The electrocardiogram (ECG) is a commonly available basic diagnostic modality in in-patient, out-patient, and emergency departments. In patients with coronary artery disease (CAD), the presence of a fragmented QRS (f-QRS), which is an extra R wave (R′), notching of the single R wave, notching of the S wave in at least two contiguous leads on the 12-lead ECG, is associated with a myocardial scar from previous myocardial injury. Furthermore, the presence of f-QRS has been shown to be associated with adverse outcomes in CAD and non-CAD patients. In the present paper, we will solely focus on the usefulness and utilization of f-QRS in predicting ventricular tachyarrhythmia in many heart diseases, that is, ischemic cardiomyopathy, non-ischemic cardiomyopathy, hypertrophic obstructive cardiomyopathy, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy. In the majority of such cases, ventricular tachyarrhythmia results in sudden cardiac death. Diagnosing them beforehand can lead to prevention and/or early treatment of these arrhythmias to prevent potential morbidity and mortality.

Keywords: *QRS fragmentation*; *ischemic cardiomyopathy*; *Non ischemic cardiomyopathy*; *hypertrophic obstructive cardiomyopathy*; *brugada syndrome*; *arrhythmogenic right ventricular cardiomyopathy*

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The 12-lead electrocardiogram (ECG) has been the first-line diagnostic test and a very valuable tool for diagnosing myocardial perfusion abnormalities. Especially, in this era of increasing incidence of non–ST-segment elevation myocardial infarctions (NSTEMI), a timely done ECG helps in deciding further management, whether urgent coronary intervention or medical management alone. Though less studied, one of the important markers in the 12-lead ECG is a fragmented QRS (f-QRS) pattern/complex. f-QRS complex may be defined as 'various RSR' patterns with or without Q waves on a 12-lead ECG' (1). Various RSR' patterns include an extra R wave (R') or notching in the nadir of the S wave, or the presence of >1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory. Based on their duration, they are sub-classified into fragmented narrow QRS complexes with duration less than 120 ms and fragmented wide QRS complexes with QRS duration more than 120 ms. f-QRS is a sign of a depolarization abnormality, found to be associated with myocardial scarring, ischemia, and fibrosis and is caused by the deterioration in the electrical signal propagation and ventricular depolarization (2, 3). The presence of f-QRS in the background of coronary artery disease (CAD) is not only known to be significantly associated with left ventricular dysfunction and impairment of myocardial perfusion but also can predict adverse cardiac events in future (4–8). Since there is recent literature on diagnosing perfusion abnormalities and the advent in latest diagnostic modalities has made it simpler to diagnose and treat these patients accordingly, relatively less effort has been made in the prevention strategy to predict bad outcomes in these patients, earlier in the course of disease. f-QRS can be a relatively cheaper and accessible marker in modern cardiology and help decrease the cost of health care expenditure by predicting bad outcomes in a high-risk population (Fig. 1).

Pathophysiology of arrhythmogenicity related to f-QRS

The QRS complex represents ventricular depolarization on the 12-lead ECG. Similarly, fragmentation of the QRS complex is associated with abnormal depolarization or myocardial scar tissue as examined in small studies (9, 10) and in computer models (11). This concept was also

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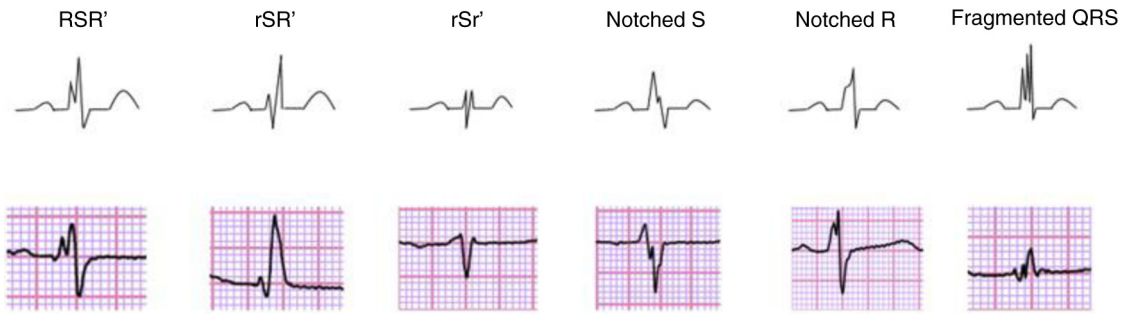

Fig. 1. Few morphologies of QRS fragmentation.

supported by studies with spectral analysis of high-frequency electrograms that revealed increased notches or 'slurring' in the electrograms after myocardial injury (12). In addition, wide-band recording in patients with CAD revealed more notches in the R wave and slurs in the S wave in those with a myocardial scar (1). This mechanism of fragmentation of QRS complex is confirmed by the autopsies of patients with myocardial infarction (MI) and left ventricular aneurysm (with confirmed presence of significant myocardial necrosis), which displayed slow activation as a result of the partially depolarized and depressed action potential upstrokes. Different shapes and morphologies of f-QRS are seen depending upon change in the QRS vector during depolarization, in and around the areas of ischemic myocardium. This change in structural and functional characteristics of myocardium results in changes of the conduction pattern, leading to the slow conduction in the myocardial scar tissue. This abnormal myocardium which may be a substrate for re-entry for an electrical impulse which originates from the atrium, and while passing through this potential area, leads to malignant ventricular arrhythmias. Hence, f-QRS, which represents the scar tissue, reflects significant underlying myocardial disease with an arrhythmic substrate (Fig. 2).

f-QRS as an arrhythmogenic marker in ischemic cardiomyopathy

Ischemic cardiomyopathy is the most common cause of heart failure (HF) in developed countries (13). The extent of CAD by angiography is prognostically more significant than sole clinical diagnosis of an ischemic cardiomyopathy (14). Ventricular tachycardia, ventricular arrhythmias, and sudden cardiac death (SCD) are major sequelae of ischemic cardiomyopathy, the prevention of which reduces the morbidity and mortality. In these patients, the f-QRS complex has been associated with regional myocardial damage, increased cardiac adverse events, and decreased event-free survival (1, 4, 5, 15). f-QRS has been shown to be associated with significantly greater perfusion and function abnormalities than the Q wave, and, in fact, the f-QRS may be the only evidence of a prior silent MI (1). In the present era, when aggressive risk factor modification is the center of focus, the sensitivity of the Q wave (36.3%) was shown to be less than half when compared with the sensitivity of the f-QRS (84.6%) to predict a remote MI (1). Similarly, considering it as a predictive marker of future cardiac arrhythmias, it was also found that the incidence of an arrhythmic event was significantly higher in the patients with f-QRS than those without f-QRS on a 12-lead ECG during mean follow-up of 17 months, and the patients without f-QRS have a higher survival probability after an arrhythmic event (16). The f-QRS represents delayed activation in a larger ventricular mass that can cause multiple spikes within the QRS complex; so delayed activation causes delayed conduction, then arrhythmia (Fig. 3).

f-QRS as an arrhythmogenic marker in non-ischemic cardiomyopathies

Non-ischemic cardiomyopathy is the damage to the structure and/or function of a heart with intact blood supply,

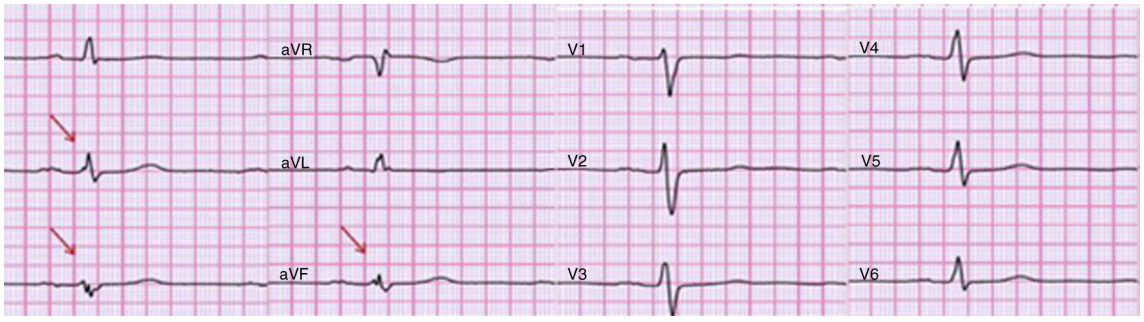

Fig. 2. 12-Lead ECG showing QRS fragmentation in inferior leads representing the diseased myocardium in specific coronary territory.

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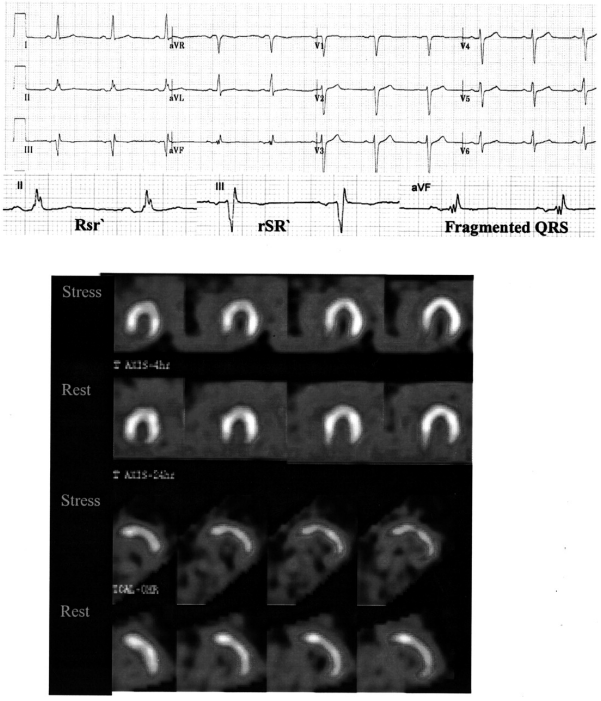

Fig. 3. 12-Lead ECG center showing normal width f-QRS in inferior leads that is correlated with an inferior wall myocardial infarction on a myocardial perfusion study. There is no Q wave. Nuclear imaging revealed a fixed inferior defect. Courtesy of MK Das (1).

and it includes dilated, hypertrophic, restrictive cardiomyopathies, and so on. f-QRS is also found to be associated with intra-ventricular dyssynchrony in non-ischemic cardiomyopathy patients with a narrow QRS interval, and this irregular activation of ventricles can lead to arrhythmias. To find the intra-ventricular dyssynchrony, studies showed that f-QRS complex was highly sensitive (90.6%) with negative predictive value (85%) in patients with non-ischemic dilated cardiomyopathy (DCM) and a narrow QRS (17). These findings are in agreement with the study by Yu et al. (18), who examined the association between intra-ventricular dyssynchrony and f-QRS complexes in patients with a wide QRS interval. Premature ventricular complexes (PVCs) without underlying heart disease may be associated with ventricular tachycardia (VT), and elimination of these PVCs with catheter ablation prevents further occurrence of VT (19). Studies have shown that the presence of f-QRS is associated with frequent PVCs in patients without overt structural heart disease (20). Predicting the bad outcomes associated with intra-ventricular dyssynchrony, Sha et al. revealed that f-QRS and sustained VT or VF (ventricular fibrillation) on ECG predict a poor prognosis in patients with idiopathic DCM (21). In this study, the incidence of ventricular tachyarrhythmia and all-cause mortality in patients with f-QRS was significantly high as compared with patients without f-QRS on their ECG (23.5% vs. 3.4%, $p = 0.043$) during follow-up of 14 ± 5 months (21). Wang et al. (16) reported 21 cases in which the combined appearance of f-QRS and J wave (a repolarization abnormality) was associated with an increased risk of idiopathic VF. Similarly, Das et al. (22) calculated arrhythmic events and all-cause mortality in 105 patients (age 58.7 ± 15.5 years; male, 70) with non-ischemic cardiomyopathy who received an implantable cardioverter defibrillator (ICD) for primary and secondary prophylaxis. In his study, f-QRS was present in 54 (51%) patients and over a mean follow-up of 21.6 ± 21.9 months, 29 (53.4%) patients in the f-QRS group received ICD therapy (anti-tachycardia therapy and/or ICD shock) when compared with only five (10%) patients in the non f-QRS group ($p < 0.001$). The combined endpoint of ICD therapy and mortality was also significantly higher in the f-QRS group when compared with the non-f-QRS group (70% vs. 17.6%, $p < 0.001$). Mortality was 24% in the f-QRS group and 14% in the non-f-QRS group ($p = 0.18$). Event-free survival was significantly decreased in the f-QRS group versus the non-f-QRS group. Based on these results, he also proposed that f-QRS is associated with significantly decreased time to the first arrhythmic event (23). It can safely be assumed that more the leads with f-QRS, the more the scar tissue in myocardium, indicating a likely worse prognosis. To better examine this association, more randomized studies are needed. In fact, there is more literature on the possible utility of f-QRS in non-ischemic cardiomyopathy when compared with its ischemic counterpart. As a marker of dyssynchrony in ischemic and non-ischemic cardiomyopathy, further studies on f-QRS might lead to identification of patients who may benefit from cardiac resynchronization therapy (CRT) to restore the normal and coordinated pumping action of both ventricles, leading to a reduction in symptoms and an improvement in survival (17).

f-QRS as an arrhythmogenic marker in ARVD/C

The role of f-QRS is not only limited to the acquired cardiac conditions but also has been debated in few congenital heart diseases which can make it an important screening marker in individuals who are at risk of SCD. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by life-threatening ventricular arrhythmias secondary to fibro-fatty replacement of the myocardium. Clinical diagnosis of ARVC is based on standard (24) and modified (25) diagnostic criteria, including depolarization and repolarization abnormalities in ECG. Depolarization abnormalities are defined as right precordial QRS prolongation ≥ 110 ms and right precordial epsilon potentials which are located between the end of the QRS complex and the beginning of the T wave (26). Modified diagnostic criteria also include prolongation of the S-wave upstroke in right precordial leads ≥ 55 ms (27). In many cases, prolonged S-wave upstroke is caused by fragmentation of the end of the QRS complex, not always

clearly distinguishable from epsilon potentials (28). This is the reason why Cox and his colleagues described terminal activation delay of $\geq$55 ms as a new ECG criterion of ARVC (29). In 2006, epsilon-like potentials that occur because of fragmentation at the beginning, on top, or at the end of the QRS complex ('pre-, top-, and post- epsilons') in different leads were presented by Zhang et al. as typical ECG findings in ARVC (30). Similarly, Peters et al. identified f-QRS as one of the markers of the ARVC as he studied the value of f-QRS in a standard 12-lead ECG in 360 patients with ARVC (176 men, mean age: 47.3 $\pm$ 13.7 years) and compared its presence with the detection of the epsilon wave in highly amplified right precordial and modified limb leads in a subgroup of 207 patients (24). f-QRS was found in 85% of patients and 4% of controls, whereas epsilon waves in highly amplified right precordial and modified limb leads could be found in 77% of the patients. Other ECG signs of ARVC include QRS prolongation, prolonged S-wave upstroke, terminal activation delay, and epsilon potentials. Summarizing the above discussion, it can be safely assumed that f-QRS can act as a reliable marker to diagnose ARVD, along with epsilon waves and T-wave inversions, and by accurately diagnosing this patient population earlier in the course of disease, primary and secondary prevention by ICD can be considered to prevent SCD.

f-QRS as an arrhythmogenic marker in Brugada syndrome

Brugada syndrome (BrS), a form of idiopathic VF, is characterized by an ECG pattern consisting of ST-segment elevation in right precordial leads with right bundle branch block-like morphology. One third of these patients present with SCD (31). BrS is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of SCDs in patients with structurally normal hearts (32). Morita et al. (33) showed a 43% incidence of f-QRS in 115 patients with BrS. The incidence of f-QRS was significantly higher in the VF group among Brugada patients when compared with the syncope or asymptomatic groups. Interestingly, the SCN5A mutation (a gene found in BrS, which encodes the alpha subunit of cardiac sodium channel) occurred more often in patients with f-QRS (33%) than in patients without f-QRS (5%) (34). In patients with syncope or VF, only 6% of patients without f-QRS experienced VF during a 43-month follow-up, whereas 58% of patients with f-QRS had recurrent syncope caused by VF ($p < 0.004$). These studies, although with a small patient population, show that since f-QRS is commonly found in BrS, it can serve as a marker for diagnosis and higher incidence of VF in the f-QRS group when compared with the non-f-QRS group, and can help classify these patients as high-risk patients warranting early intervention to prevent these life-threatening arrhythmias.

f-QRS as an arrhythmogenic marker in hypertrophic obstructive cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) is the most common genetic heart muscle disorder causing myocardial hypertrophy in the absence of abnormal conditions, for example, hypertension or high volume states (35, 36). This diagnosis has been a great challenge because of its initial presentation as SCD involving young and asymptomatic people including trained athletes. 12-Lead ECG is one of the non-invasive tests to evaluate these patients but until now no specific criterion has been reported to be valuable for risk stratification (36, 37). Femenia and his colleagues (38) aimed a study to determine whether f-QRS in the surface ECG could predict arrhythmic events in a retrospective multicenter study, using appropriate therapy delivered by the ICD as a surrogate. They showed that f-QRS is highly prevalent in patients with HOCM and moreover the presence of f-QRS was associated with a worse prognosis predicting arrhythmic events in patients who receive ICD for primary or secondary prophylaxis of SCD. Recently, magneto-cardio-graphic analysis of 11 (10 with f-QRS) patients with HOCM, narrow QRS, and ICD implants revealed that left ventricular conduction time was markedly prolonged in HOCM patients compared with controls (81 vs. 51 ms, $p \leq 0.001$). The authors concluded that patients with HOCM and history of life-threatening ventricular arrhythmias often showed intra-QRS fragmentation on ECG which emphasizes the importance of f-QRS as a valuable marker to identify these high-risk patients for lifesaving primary and secondary preventive therapy such as ICDs (39–41).

Summary and future direction

f-QRS is a simple, inexpensive, and readily available ECG sign that can be interpreted easily by clinicians. Researchers have examined f-QRS as a diagnostic marker and its potential to predict arrhythmic events in the above-mentioned ischemic as well as non-ischemic diseases, having arrhythmia as a hallmark sequela. f-QRS may be of great value in determining the high-risk population in these diseases to treat them aggressively and prevent them from experiencing life-threatening arrhythmias leading to SCD. It can also help in guiding selection for device therapy in patients with structural or functional heart disease whether it is ischemic, non-ischemic, or genetic. However, f-QRS is a non-specific marker whose diagnostic, predictive, and prognostic value should only be calculated in the presence of relevant clinical evidence along with the type of myocardial disease, for example, structurally abnormal versus structurally normal heart.

To better understand the mechanism of pro-arrhythmogenicity, coordinated efforts in genetics, molecular science, translational research, and clinical studies focusing on the physiological and pathological mechanisms of f-QRS are needed. Its utility in risk stratification of

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life-threatening arrhythmia needs to be explored further. It is possible to enhance the predictive value of f-QRS for arrhythmias by analyzing it with other markers of repolarization abnormalities such as ST-T wave changes, Q waves, and J point elevation.

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