Introduction

Presence of subtle abnormality within the QRS complex is associated with myocardial scarring, ischemia and fibrosis which is due to the signal conduction disturbance and ventricular depolarization abnormalities [1]. Fragmentation originates from injured tissue around an infarct scar where ventricular activation is delayed and asynchronous resulting in the RSR' pattern of the QRS complex in 12-lead Electrocardiography [2]. Fragmentations of QRS are more common among the patients with prior myocardial infarction and with patients with either right or left ventricular enlargement. Das et al. [3], demonstrated, fragmented QRS complex in patients with coronary artery disease (CAD) was associated with ventricular conduction delay due to myocardial scar detected by myocardial single photon emission tomography (SPECT) [3]. FQRS in patients with known coronary artery disease has emerged as the independent predictor for major adverse cardiac events (MACE) and all-cause mortality [1].

Myocardial scar is also a substrate for reentrant ventricular tachyarrhythmia. A signal averaged electrocardiogram (SAECG) reveals the presence of abnormal late potential which represents a slow conduction zone with damaged myocardium around the fibrosis of healed myocardial infarction [4]. The presence of late potential has been used for risk stratification of sudden cardiac death or lethal arrhythmic events. As well as SAECG, fQRS also can reflect intra-cardiac conduction abnormality and will represent a substrate for ventricular arrhythmia [5]. But it is still unknown whether there is a correlation between fQRS and late potential in other diseases such as CAD and various cardiomyopathies.

Definition of fQRS

The routine 12-lead ECG recording (high-pass filter: 0.05-20 Hz, low-pass filter: 100-150 Hz, AC filter: 50 or 60 Hz, paper speed: 25-50 mm/sec and voltage: 1 mm/mV) is used to detect fQRS [3]. There is no special setting required for the recording of fQRS. Fragmented QRS complex is categorized into narrow fragmented QRS complex (f-nQRS) and wide fragmented QRS complex (f-wQRS).

Narrow Fragmented QRS Complex

FQRS on a 12-lead ECG was originally defined as narrow QRS complex duration (<120 ms). Das et al. [3] 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. Typical bundle branch block (BBB)
pattern (QRS ≥ 120 ms) and incomplete right BBB were excluded from their original definition [3].

**Fragmented Wide QRS Complexes**

Wide QRS include QRS complexes due to bundle branch block (BBB), or premature ventricular complexes (PVC) and paced QRS. Das et al. [6], defined f-wQRS as QRS duration ≥ 120 ms in 2 or more contiguous leads. (Figure 2) fragmented BBB, fragmented PVC and fragmented pQRS are the subtype of f-wQRS.

**Fragmented BBB:** Fragmented Right BBB (RBBB) or left BBB (LBBB) is defined as (QRS duration ≥ 120 ms) with various RSR' patterns with or without a Q wave, with >2 R waves (R') or >2 notches in the R wave, or >2 notches in the down stroke or upstroke of the S wave, in 2 contiguous leads corresponding to a major coronary artery territory.

**Fragmented PVC:** Fragmented PVC is defined by the presence of >2 R' or >2 notches in the S waves in 2 contiguous leads. In addition, f-PVC also included PVCs with only 2 notches in the R wave but were >40 ms apart and present in 2 contiguous leads [7].

**Fragmented pQRS:** Paced QRS (pQRS) is defined as a wide QRS complex (duration >120 ms and without any evidence of QRS fusion) initiated by a paced spike in patients with a pacemaker or ICD. Fragmented paced QRS (f-pQRS) is defined by the presence of >2 R’ or >2 notches in the S waves in 2 contiguous leads.

**Mechanism of Fragmentation**

Several studies have suggested that fragmentation of QRS occurs due to an alteration of the normal depolarization of the ventricles. Autopsies of patients with MI and LV aneurysm have confirmed significant myocardial necrosis, with “islands” of viable myocardial tissue interspersed in abundant fibrous tissue [6]. The islands of chronically ischemic myocardium display slow activation as a result of partially depolarized and depressed action potential upstroke velocities. This feature is responsible for inhomogeneous activation of the ventricles. This alters ventricular depolarization patterns, as shown by endocardial mapping and computer models, probably represent fragmentation in the QRS complex on the surface 12-lead ECG [8].

**Electrophysiology of Fragmented Wide QRS Complexes**

Normal ventricular depolarization occurs in 3 phases, involving the interventricular septum (phase 1), free wall of right ventricle (phase 2), and free wall of left ventricle (phase 3). Phases 2 and 3 normally occur simultaneously and are in almost opposite directions. As a result, only the net vector is registered on the surface ECG. In the presence of RBBB, phase 2 is delayed occurring after phase 3 resulting in prolongation of the QRS duration. Additionally, the right ventricular depolarization produces a higher voltage potential on the surface ECG, due to the absence of the opposing effect of simultaneous LV depolarization. This vectorially unopposed activation of right ventricle leads to a diminished S wave depth in V1, which may even disappear completely depending on the severity of the conduction abnormality. Therefore, ECG changes in RBBB are mainly a prolongation of QRS duration and a delayed terminal depolarization manifested as an R’ wave along with reduced S waves in V1 and V2 as well as a prominent slurred S wave in I, V5, and V6. A similar but vectorially opposite phenomenon occurs in LBBB and is manifested as RSR’ pattern in the left precordial leads. Similarly, the PVC morphology also depends on the site of origin and the physiology of intramyocardial conduction. PVCs in patients with structurally normal hearts have a wide QRS with a smooth contour of the R wave or a narrow notch <40 ms in the R wave [9]. Likewise, right ventricular pacing is usually from the right ventricular apex and, therefore, it depolarizes the left ventricle similar to a PVC (LBBB, left superior axis) originating from that area.

**Fragmented QRS Complex and Myocardial Scar**

Das et al. [3], compared sensitivity and specificity of Q wave and fQRS for detecting myocardial scar in a cohort of 479 consecutive patients with and without prior history of coronary disease who were referred for nuclear stress test. In this analysis, fQRS complexes have higher sensitivity than Q waves for detecting regional myocardial scar as well as detecting myocardial scar independently of the regional correlation (fQRS vs Q wave: 85.6% vs 36.3%). However, when comparing specificities, fQRS was less specific than Q wave for myocardial scar (85.6% vs 99.2%). In a cohort of 879 patients with wide QRS (equal or more than 120 ms, including BBB, PVC, or paced QRS), referred for nuclear stress testing or cardiac catheterization for evaluation of coronary artery disease (CAD), presence of fragmented wide QRS complex was associated with high sensitivity, specificity of myocardial scar and high positive predictive value, negative
predictive value (86.8%, 92.5%, 92%, and 87.5%, respectively). When analyzing outcome data, fQRS was associated with an increased risk of all-mortality after adjustment for age, ejection fraction (EF) and history of diabetes mellitus [6]. In another cohort of 56 patients, fQRS seemed to correlate with chronic total coronary occlusion with poorly developed collateral coronary circulation in patients without prior MI [10]. In contrary to those findings, 2 studies failed to show significant association between fQRS and myocardial scar. Wang at el. [11], reassessed sensitivity and specificity of fragmented QRS for detecting myocardial scar. ECG and nuclear perfusion images of 460 consecutive patients with known or suspected CAD were correlated. They found both the fragmented QRS and Q wave had poor sensitivity and specificity in detecting fixed or mixed myocardial scar. Similar results were found by Carey et al. [7] in a cohort of 138 patients with severely depressed LV systolic function (mean EF 27 ± 9%) who had infarct volume assessed by positron emission tomography [7]. In this population, fQRS was not predictive for infarct size in both patients with narrow and wide QRS complex.

**Fragmented Wide QRS Complexes and Myocardial Scar**

Fragmented narrow QRS complexes (<120 ms) on a 12-lead ECG signify an old MI scar, is associated with a poor prognosis. Das et al. [6] investigate whether myocardial scar alters the QRS morphology similar to that encountered in narrow QRS complexes and results in an additional R’ or notch in the R wave or the S wave. Typical BBB is associated with a RSR’ pattern due to partial transmural depolarization of the ventricle due to relatively slow or absent conduction of the ipsilateral bundle branch. Typically, QRS complexes due to BBB have only 1 additional R’ (or 2 notches on the wave). The different QRS morphologies probably represent intramyocardial conduction abnormalities and peri-infarction conduction block due to myocardial necrosis or scar. Myocardial depolarization during a PVC or paced rhythm occurs due to intramyocardial conduction of impulses, which typically results in a wide QRS. Several smaller studies have shown that notching and qR pattern in the contour of BBB, PVC, and paced rhythm are associated with an old MI.

**Fragmented BBB and Myocardial Scar**

Other than the Q wave, there is no diagnostic sign of an old anterior or lateral wall MI in the presence of LBBB. Furthermore, with the recent improvements in the management of acute MI, including aggressive medical therapy, the use of thrombolytic agents, and early coronary revascularization, the incidence of Q-wave MI has decreased from 66.6% to 37.5%, and the incidence of non-Q-wave MI has increased reciprocally [12]. This trend has made the recognition of an old MI in the presence of a BBB more difficult. Multiple Center Investigation of the Limit of Infarction Study demonstrated that late notching of the S wave in V1 to V3 as one of the specific ECG signs of MI in the presence of LBBB [13]. The notching of the S wave in addition to the R waves in LBBB qualifies for the definition of f-BBB. Similarly, found that, the RSR’ complex associated with a wide QRS (≥110 ms), unrelated to RBBB or LBBB was identified in 26 patients with an old MI [2]. In these patients, the RSR’ pattern was present in the precordial leads, inferior leads, or both. Severe segmental wall motion abnormalities (akinetic in 16 and dyskinetic in 10 patients) consistent with MI scar were detected using the equilibrium radionuclide study and the 2-dimensional echocardiogram in these patients. A pathological study confirmed that the Q wave and notches in the S wave upstroke or nadir represents MI scar [14].

**Fragmented PVC and Myocardial Scar**

Notching of the PVC represents myocardial scar and Moulton et al [11]. Have shown that PVC with a normal contour or notching of QRS with a separation of <40 ms is associated with no myocardial disease, whereas notch (or selves) of the QRS with a separation of >40 ms was associated with significant myocardial disease. In another study, 12-lead ECGs and 2-minute multiple-lead rhythm strips revealed PVCs in 58 of 515 patients who underwent cardiac catheterization. Twenty-one patients with PVCs had prior MI diagnosed by regional akinesia or dyskinesia on left ventriculography [15]. Standard criteria were used to diagnose prior MI from the sinus beats of the ECG. MI was diagnosed when a PVC had a Q or QRS pattern with Q wave ≥0.04 seconds. Morphological analysis of PVCs had a low sensitivity (29%) but high specificity (97%) and high predictive value (86%) for the diagnosis of MI, whereas a Q wave in sinus rhythm had a sensitivity of 52% and specificity of 97%. Similarly study by Das et al. [7] has shown that f-PVC has a much higher predictive value for diagnosing MI scar.

**Fragmented pQRS and Myocardial Scar**

The usefulness of the 12-lead resting ECG is limited for diagnosing an old MI in paced ventricular rhythms [16]. In a study of 45 patients with MI (anterior 23, inferior 22) and 26 healthy controls, pacing was applied from the right ventricular apex after coronary angiography [17]. The sensitivity, specificity, and average diagnostic accuracy of the 5 known criteria for MI scar in the presence of paced ECG were assessed. These include (1) notching (0.04 second in duration) in the ascending limb of the S wave of leads V6, V5, or V4, (Cabrer’s sign); (2) notching of the upstroke of the R wave in lateral leads (I, aVL, or V5, Chapman’s sign); (3) Q waves >0.03 second in duration in lateral leads; (4) notching of the first 0.04 second of the QRS complex in inferior leads (II, III, and aVF); (5) Q wave >0.03 second in duration in inferior leads. The most sensitive criteria, for anterior and inferior MI were Cabrera’s and Chapman’s (91.1% and 86.6%, respectively). All criteria had a low specificity (range, 42.3% to 69.2%). The combination of Cabrera’s and Chapman’s sign decreased the sensitivity to 77.7%, but increased the specificity to 82.2%. A recent study (n=107) revealed that Cabrera’s sign (63.6%) was a moderately sensitive sign for MI scar but other known ECG signs had a poor sensitivity (9.1% to 40.9%) [18]. However, the specificity (81.6% to 100%) was relatively high for all ECG. Das et al. [7], study also show f-pPVC (>2 QRS notches), with a sensitivity of 89.7% and a specificity of 95.7%.

**Fragmented QRS as a Predictor of Mortality and Adverse Cardiac Events**

Since fQRS represents myocardial scar, fQRS may be associated with heart failure and ventricular tachyarrhythmia. Some studies have shown a relationship between existence of fQRS in patients with CAD and prognosis. Cohort study conducted by Das et al. [1], demonstrated that, the presence of fQRS was associated with higher all-cause mortality (34% vs 26% in patients without fQRS) and cardiac event rate defined as MI, cardiac death and need for revascularization (50% vs 28% in patients without fQRS). In the multivariate Cox regression analysis, fQRS was independent predictor of cardiac events (HR 1.62; p = 0.0001) but no all-cause mortality (HR 1.07; p = 0.62). Pietrasik et al. [19], studied patients with first Q-wave MI and effect of fQRS, resolved Q wave, and persistent Q wave on 2 month follow-up ECG on the risk of recurrent cardiac events.
defined as unstable angina, recurrent MI or cardiac death. In this study, presence of fragmented QRS independently of Q waves was not associated with, increased risk of recurrent events in the general population of patients after MI. However, among patients with resolved Q waves, fragmented QRS was associated with increased risk of cardiac events. It was proposed that fQRS may identify ischemic myocardium.

Patients with organic heart disease often have right or left BBB, and wide QRS complexes are associated with adverse prognosis for the patients. The HERO-2 trial showed that mortality of patients who had left/right BBB with anterior AMI or patients who had right BBB with inferior AMI was higher than that of patients with AMI but no sign of BBB [20]. Das et al. [1], showed that wide QRS is associated with a significantly higher mortality when compared with its absence (P=0.017) during a mean follow-up of 29 months. The study results are in concordance with the mortality rates reported in patients with a narrow fQRS (<120 ms) [19]. A large-scale study involving 46,933 veterans revealed that BBB and paced QRS were predictors of cardiovascular mortality S [21]. Similarly, many other studies have shown that wQRS itself is a predictor of mortality in patients with CAD, but this study further identifies f-wQRS as a marker of the higher risk population (f-BBB, f-PVC, and f-QRS) in the wQRS group [22,23]. fQRS is also associated with significantly higher arrhythmic events in patients with an ICD [24]. Therefore, it is possible that f-wQRS, which represents abnormalities of impulse conduction, may create a milieu for malignant reentrant ventricular arrhythmias and death.

A study in which fQRS was evaluated by a body surface mapping system also showed that fQRS was an independent predictor for cardiac death and hospitalization due to heart failure in patients with prior myocardial infarction [25]. Torigoe et al. [26], evaluated fQRS by 12-lead ECG and showed that the number of the leads with fQRS was a predictor for cardiac death and hospitalization for heart failure in patients with prior myocardial infarction [26]. Although prior criteria for positive fQRS included the presence of fQRS in 2 or more contiguous leads, they showed that the presence of fQRS in 3 or more leads was the most useful for distinguishing between patients with and without risk for cardiac death or hospitalization. An increase in the number of leads with fQRS would represent a wide scar area, which would result in an adverse outcome. FQRS also predicted intra- and post-operative hemodynamic instabilities and adverse cardiovascular events in patients undergoing coronary artery bypass graft surgery [20].

**Summary**

Presence of fragmented QRS in cardiovascular disease is related to myocardial scar/myocardial ischemia or myocardial fibrosis which is due to the abnormalities of conduction and depolarization process within ventricles. FQRS is a valuable ECG marker of myocardial scar and can predict major adverse cardiac events and mortality in patients with acute coronary syndrome. However, the predictive value of its ECG marker seems to be different in different populations. Various studies demonstrated different degree of sensitivity of fragmented QRS. But the limitation of its utility is mainly due to subjective assessment of fQRS. For better prediction of prognosis and improvement of diagnosis, objective evaluation and qualitative analysis of fQRS is required. One of the future directions for qualitative analysis of depolarization process is an analysis of high frequency QRS components possibly by magneto-electrocardiography.

**References**


