Role of the Fragmented QRS Complexes on a Routine 12-lead ECG in Predicting Mortality and Sudden Cardiac Death

MITHILESH K. DAS, MD, DOUGLAS P. ZIPES, MD

SUMMARY

Several invasive and noninvasive tests for risk stratification of sudden cardiac death (SCD) have been studied. Except for left ventricular ejection fraction, very few markers of SCD can be utilized routinely in clinical practice due to the lack of a desirable predictive value. The presence of fragmented QRS complexes (fQRS) on a routine 12-lead ECG is a marker of depolarization abnormality secondary to myocardial scar. fQRS is associated with increased mortality and ventricular arrhythmic events in patients with chronic coronary artery disease and in acute coronary syndrome. fQRS also predicts arrhythmic events in ischemic and nonischemic cardiomyopathy. In Brugada syndrome, the presence of fQRS predicts episodes of ventricular fibrillation during follow-up. fQRS may be of value in determining the risk for SCD and guiding selection for device therapy in patients with structural heart disease and Brugada syndrome. It is possible that the predictive value of fQRS for SCD can be enhanced further by combining it with a marker of repolarization abnormality, such as microvolt T wave alternans. The purpose of this review is to discuss the potential utility of fQRS for the risk stratification of mortality and SCD.

INTRODUCTION

Several invasive and noninvasive tests for risk stratification of sudden cardiac death (SCD) have been studied (1) mostly in the high-risk population with known heart disease such as structural heart disease or inherited arrhythmia syndromes. However, the majority of episodes of SCD actually occur in those with low- to intermediate-risk factors who have minimal or no known heart disease. (2) Except for left ventricular ejection fraction (LVEF), few markers of SCD can be utilized routinely in clinical practice. The major limitation of these tests is their lack of a desirable positive predictive value for SCD. This makes the risk stratification of SCD very challenging. Malignant ventricular arrhythmias such as sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are responsible for two thirds of SCD. (3) The majority of ventricular arrhythmias are reentrant in nature. For a reentrant arrhythmia to sustain, an abnormal repolarization of the tissues and/or disorder of impulse conduction are required. These can be detected as repolarization and depolarization abnormalities of the heart by various invasive and noninvasive tests. Repolarization abnormalities such as the microwave T wave alternans (MTWA), QT prolongation and QT dispersion are predictors of SCD. Depolarization abnormalities that predict SCD are late potentials on signal averaged electrocardiography and wide QRS, as well as fragmented QRS complexes (fQRS) (4) on routine 12-lead ECG. We demonstrated that the fQRS represents conduction delay due to myocardial scar in
patients with CAD. However, fQRS is not specific for CAD and is also encountered in other myocardial diseases such as nonischemic dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C) (5) and Brugada syndrome. (6) The purpose of this review is to discuss the potential utility of fQRS for the risk stratification of mortality and SCD.

We defined fQRS on the routine 12-lead ECG (filter range, 0.15 to 100 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mV) which includes various morphologies of the QRS wave with or without a Q wave. (4, 7) fQRS includes 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 artery territory (Figure 1). (4) Typical bundle-branch block pattern (QRS ≥ 120 ms) and incomplete right bundle-branch block were excluded from the definition of fQRS. Later, we extended the definition of fQRS in the presence of wide QRS complexes (QRS ≥ 120 ms), such as bundle branch block (BBB), premature ventricular complexes (PVCs) and paced QRS complexes (pQRS). (8) To define fragmentation in wide QRS complexes (f-wQRS), we added a criteria of >2 notches in the R or the S wave, since bundle branch blocks already have two notches or peaks present in two contiguous leads. (Figure 2)

1. SIGNIFICANCE OF fQRS IN VARIOUS HEART DISEASES:

a. Coronary artery disease (CAD): We demonstrated that the fragmentation of QRS complexes, both narrow (QRS duration <120 ms) (4) and wide (QRS duration ≥ 120 ms), (8) represent myocardial scar in patients with suspected or known CAD. Sensitivity, specificity, and the negative predictive value for myocardial scar were 86%, 89%, and 93%, respectively, for the fQRS, and 91%, 89%, and 94%, respectively, for the Q wave. In another study of 879 patients with wide QRS complexes, we showed that fragmented wide QRS (f-wQRS) represents myocardial scar. (8) The sensitivity, specificity, positive predictive value and negative predictive value of f-wQRS for myocardial scar were 87%, 93%, 92% and 88%, respectively.

b. Non-CAD:

i. Dilated cardiomyopathy (DCM): In patients with DCM, QRS fragmentation has been recorded during wavelet ECG analysis recorded from 6 unipolar left precordial leads, using a high-precision amplifier. (9) When compared with the control subjects with no heart disease, these wavelets predicted frequent premature ventricular complexes and SCD. In DCM, fQRS signifies myocardial scar defined by gadolinium delayed enhancement on cardiac magnetic resonance imaging. fQRS also signifies myocardial scar in non-CAD patients. In a study by Das et al, fQRS was encountered in nearly half of the patients with nonischemic dilated cardiomyopathy (DCM) who received an ICD for primary or secondary prevention of SCD. (10)
ii. Cardiac sarcoidosis: Homsi et al, demonstrated that fQRS is a risk marker of cardiac sarcoidosis. (11) The sensitivity and specificity of fQRS for detecting abnormal gadolinium-delayed enhancement images in cardiac magnetic resonance imaging were 100% and 80%, respectively, whereas the sensitivity and specificity of Q waves in that study were 11% and 100%, respectively.

iii. ARVD/C: fQRS has been identified as a risk marker of ARVD/C by Peters et al They studied the value of QRS fragmentation in a standard 12-lead ECG in 360 patients with ARVD/C (176 men, mean age: 47.3 ± 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. (12) In this study, 52 phenotypically and genotypically nonaffected subjects from systematic family screening in 10 families with known plakophilin-2 and desmoplakin mutations served as controls. fQRS 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 ARVD/C include QRS prolongation, prolonged S-wave upstroke, terminal activation delay, and epsilon potentials. Most of these signs are incorporated in typical fQRS. fQRS will probably simplify the ECG diagnosis of ARVD/C in patients with a high probability of the disease.

2. fQRS AS A PREDICTOR OF MORTALITY IN CAD:

a. Chronic CAD: In a study of 998 patients who were evaluated for CAD, the all-cause mortality (34% vs. 26%) and cardiac event (MI, cardiac death, need for revascularization) rate (50% vs. 28%) were significantly higher in patients with fQRS compared to patients without fQRS, during a mean follow-up of 57 months.2 Kaplan-Meier survival analyses revealed a significantly lower event-free survival for cardiac events ($P < .001$) and all-cause mortality ($P = 0.02$). (Figure 3) Although the fQRS did not independently predict mortality in that study, the f-wQRS was an independent predictor of mortality ($p=0.017$) in another study.(8)

b. Acute coronary syndrome (ACS): In the quest to determine the time course of appearance of fQRS in patients with CAD, we studied serial ECGs of 896 acute coronary syndrome patients (mean age 62 ± 11 years, 98% men) who underwent cardiac catheterization. (13) Four hundred forty-one patients had MI (myocardial infarction), including 337 patients with non-ST elevation myocardial infarction (NSTEMI), and 455 patients had unstable angina (the control group). Serial ECGs were obtained every 6 to 8 hours during the first 24 hours after the diagnosis of MI and the next day (<48 hours). Fragmented QRS developed in 224 patients (51%) in the MI group and only 17 (3.7%) in the control group ($p < 0.001$). New Q waves developed in 122 (28%), 76 (23%), and 2 (0.4%) patients in the MI, NSTEMI, and control groups, respectively. The sensitivity values of fQRS for ST elevation MI and NSTEMI were 55% and 50%, respectively. The specificity of fQRS was 96%. Kaplan-Meier survival analysis revealed that patients with fQRS had significantly decreased times to death compared to those without fQRS. Fragmented QRS, T-wave inversion, and ST depression were independent predictors of mortality during a mean follow-up period.
of 34 ± 16 months. Therefore, fQRS is a moderately sensitive but highly specific sign for ST elevation MI and NSTEMI. Furthermore, fQRS is an independent predictor of mortality in patients with ACS.

c. Q-wave MI: Pietrasik et al. studied the predictive value of fQRS in patients with Q wave MI. In this population, fQRS predicted over twofold higher risk (adjusted HR 2.68, p = 0.004) of recurrent cardiac events (cardiac death, nonfatal MI) compared with those without fQRS and persistent Q waves. (14)

3. fQRS AS A PREDICTOR OF ARRHYTHMIC EVENT

a. Ischemic and nonischemic cardiomyopathy: We studied arrhythmic events and mortality of 361 patients (male 91%, age 63.3 ± 11.4 years, mean follow-up: 16.6 ± 10.2 months) with CAD and DCM who received an ICD for primary or secondary prophylaxis. (10) The fQRS included various RSR’ patterns (QRS duration <120 ms) including ≥ 1 R primes or notching of the R wave or the S wave present in at least two contiguous leads of those representing anterior (V1-V5), lateral (I, aVL and V6) or inferior (II, III and aVF) myocardial segments. The fQRS was present in 84 (23%) patients (fQRS group) and absent in 100 (28%) patients (non-fQRS group). Wide QRS (wQRS, QRS duration ≥ 120 ms) was present in 177 (49%) patients. Kaplan-Meier analysis revealed that event-free survival for an arrhythmic event (ICD shock or antitachycardia pacing) was significantly lower in the fQRS group as compared to non-fQRS and wQRS groups (p < 0.001 and 0.019, respectively). (Figure 4) fQRS was an independent predictor of arrhythmic event, but not the death.

Arrhythmic events treated by ICD shocks occur more frequently than SCD in patients with DCM. (15) This suggests that episodes of nonsustained ventricular tachycardia frequently terminate spontaneously in such patients.

b. Brugada syndrome: Brugada syndrome was initially thought to occur in patients with structurally normal hearts. However, depolarization abnormalities, such as abnormal SAECG and complete or incomplete right bundle branch block are frequently found in patients with Brugada syndrome. (16) Recently, endocardial mapping of the right ventricle of patients with Brugada syndrome revealed a significantly higher incidence of intracardiac fragmentation in the right ventricle (17) similar to those recorded in patients with CAD during endocardial mapping of the left ventricle. (18) The existence of LP on SAECG suggests the presence of regions undergoing depolarization later than most of the ventricle, and thus it is a marker of myocardial conduction abnormalities. (19) Recently, Morita et al. demonstrated that, in patients with Brugada syndrome, the incidence of fQRS was significantly higher in patients with VF as compared to the syncope or asymptomatic groups (incidence of fQRS: VF 85%, syncope 50%, and asymptomatic 34%, p <0.01). (6) LPs have been reported to occur frequently in patients with Brugada-type ECG (20, 21), however, VF can also occur in patients without LPs (16).

Mechanisms of fQRS in arrhythmogenesis
The mechanism of fQRS on the routine 12-lead ECG is speculative. Fragmentation of QRS has been
implicated with inhomogeneous activation of the ventricles due to myocardial scar and/or ischemia, which predict arrhythmic events as well as death. (4, 22-24) Earlier publications have defined notching of the QRS wave after a myocardial infarction as peri-infarction conduction block, which can also be defined as fQRS. (25) The possible mechanism of fragmentation is supported by autopsies of patients with MI and left ventricular aneurysm, which confirmed the presence of significant myocardial necrosis, with “islands” of viable myocardial tissue interspersed in abundant fibrous tissue. (26, 27) Endocardial and epicardial mapping in CAD and DCM patients with ventricular arrhythmias have revealed fractionated electrograms over a wide area surrounding the myocardial scar. (18, 28) Papillary muscles from hearts from patients with CAD who had undergone transplantation also revealed slow conduction through the muscle bundles separated by interstitial fibrosis causing a “zigzag” path, with delayed intramyocardial conduction which, in turn promotes reentry. (29) Similarly, hearts from patients with DCM who had undergone transplantation also revealed fractionated electrograms recorded in the diseased myocardium were due to both distinct, long strands and short stretches of fibrous tissue. Delayed conduction was caused by curving of the activation around the distinct lines of block and by the wavy course of activation between the short barriers. (30) The latter reflects extreme nonuniform anisotropy. The presence of myocardial scars is probably the cause of localized conduction block leading to additional R prime or notching of the S wave or the R wave. Abnormal SAECG indicates any intraventricular conduction delay or altered depolarization patterns occurring during early and mid QRS that may not extend beyond the J point which marks the end of depolarization on a 12-lead ECG. A disorganized ventricular depolarization is caused by an abnormal spatial and temporal pattern of impulse conduction in the presence of pathological substrate in the ventricles. Therefore, fragmentation of QRS can occur in early, mid and late phases of the QRS wave. Morita et al, demonstrated that fQRS may or may not coexist with LP in patients with Brugada syndrome. (6) Flowers et al, have shown that the extent of late potentials on SAECG in patients with the peri-infarction exceeded those found in patients without peri-infarction block (p < 0.0001). There was a significantly higher incidence of sustained ventricular arrhythmias and SCD in patients with peri-infarction block on the surface ECG. 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. (31)

Brugada syndrome is an example of combined depolarization and repolarization abnormality. (6) Endocardial mappings have revealed that the type 1 Brugada syndrome patients had longer right ventricular activation times and QRS intervals (both are depolarization abnormalities) compared to type 2 Brugada syndrome and controls in that study. Additionally, endocardial repolarization abnormalities were also demonstrated in these patients during electroanatomical mapping by showing that the mean activation recovery interval corrected for heart rate as a measure of action potential duration was significantly lower than the controls. In the type 1 Brugada syndrome patients, the combination of increased fragmentation, slowed activation and shortened recovery indicates asynchronous and slowed impulse transmission but fast recovery. This may be an important contributor to the specific ECG pattern and arrhythmogenesis in Brugada syndrome. (17)

Limitations of fQRS
fQRS on a 12-lead ECG requires an optimal low pass filter setting (100 or 150 Hz). Fragmentation may be missed with a filter setting of 40 or 60 Hz. Apart from notching, slurring of fQRS may also represent myocardial scar; however, the present definition of fQRS being qualitative, prevents the incorporation of slurring in this phenomenon. A quantitative definition of fQRS with development of specific software is underway. It is to be emphasized that fQRS is a nonspecific finding and should only be interpreted in the presence of pertinent clinical evidence of myocardial scar as in CAD or primary electrical abnormalities of depolarization such as Brugada syndrome.

REFERENCES


