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Review

Is there a utility for QRS dispersion in clinical practice?

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Abstract

Prognostic markers derived from standard ECG have always been seductive. Increased dispersion of durations of the P wave, of the QRS complex, or of the QT interval has been associated with the risk of atrial fibrillation, ventricular arrhythmias, sudden cardiac death, as well as with a general negative prognosis in various settings.

However, these markers have intrinsic and methodological issues that question their utility. This paper presents data supporting the utility of QRS dispersion in clinical practice. Our investigation shows that QRS dispersion is a simple electrocardiographic marker with potential value in the assessment of patients in a variety of clinical settings: ischemic heart disease, heart failure, and cardiomyopathies.

More studies are needed to validate QRS clinical utility for predicting the risk for ventricular arrhythmias and sudden cardiac death, and for the evaluation of the response to cardiac resynchronization therapy.

Keywords: 12-lead electrocardiogram, cardiomyopathy and heart failure, myocardial infarction.

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Introduction

QRS complex refers to the combination of three of the graphical deflections seen on a typical electrocardiogram (ECG). QRS dispersion is defined as the difference between the maximum and minimum QRS duration measured in the standard twelve lead ECG. It has been suggested that an increased QRS dispersion (QRSd) is a marker of inhomogeneous ventricular depolarization and could be associated with negative prognosis (1).

Dispersion of surface ECG wave durations or intervals (P wave, QRS, QT interval, JT interval) has been assiduously studied in the search for non-invasive cardiac markers useful in predicting the risk of atrial fibrillation, ventricular arrhythmia, and sudden cardiac death, and also as nonspecific prognosis markers. The largest body of data refers to QT dispersion (QTd), but, after an initial flurry of positive results, the potential significance of QT dispersion slowly entered into obscurity, due to a number of fundamental issues (2). The most important criticism is based on the way the ECG is constructed and derived from the projection of the electrical activity loops. It has been suggested that, at least in limb leads, QT-d is an 'illusion'. Other methodological issues in QT dispersion are associated with its poor reproducibility, mostly due to the difficulty of identifying T wave offset. Some authors have extended the same arguments to P wave dispersion (3), but the question arises as to whether they also affect QRS dispersion.

As Batchvarov stated (4) ''the clinical significance of an ECG marker should be proved or disproved on the basis of its reproducibility and its link to important clinical events or other clinical variables (or lack thereof). Attempts to bolster its clinical significance by speculating about underlying electrophysiological mechanism (for example in manuscripts reporting purely clinical ECG studies) should be discouraged''.

In this paper, we review studies supporting the need for continued research into QRSd and argue that abandoning its potential utility should not occur just because of insufficient knowledge regarding its electrophysiological basis.

Discussion

Does QRS dispersion have an electrophysiological basis? Differences in excitation times of the normal human heart

Durrer et al., as early as in 1970, reviewed several studies and considered: ''knowledge of the time course and instantaneous distribution of the excitatory process of the normal human heart would be of value for understanding the QRS complex'' (5).

They studied seven re-perfused normal human hearts which were removed within half an hour after death. Electrocardiograms taken before death were not suggestive of heart disease. The hearts were maintained under physiological conditions for conducting the study, with cardiac electrical activity recorded using epicardial and intramural electrodes. The overall pattern of the left ventricle (LV) depolarization showed the synchronous excitation of 3 endocardial areas, 0-5 ms after the start of depolarization: (1) an area on the upper anterior paraseptal wall, extending toward the apex into the region anterior papillary muscle insertion; (2) a central area on the left side of the interventricular septum; and (3) the posterior paraseptal area. These areas of electrical activation extend into the next 5-10 ms, and merge at 15-20 ms after the onset of excitation. At this time, the activation front envelops a great part of the ventricular cavity except for a postero-basal area, a middle lateral area, and an apical anterior area. This movement around the cavity is much more rapid than the spread toward the epicardium. Activation of the right ventricle starts 5-10 ms after that of LV, near anterior papillary muscle insertion, then spreads to the septum and free wall.

Epicardial breakthrough is recorded in the pre-trabecular area after 20 ms, reaching pulmonary conus and the postero-basal area at 60-70 ms. The epicardial excitation pattern reflects the intramural excitation wave.

Cassidy et al. performed an endocardial mapping of the sinus rhythm in 15 patients without known heart disease (6). Their results are similar to the findings of Durrer et al.; furthermore they suggested that, after initial activation, electrical activity spreads radially and rapidly from these breakthrough points to converge at the apex and finally the infero-posterior base. The observation that the apex is activated 'relatively late' (last 25% of left ventricular endocardial activation) had not been noted previously. Left ventricular endocardial activation began at 0-15 ms after the QRS complex onset. Endocardial activation of LV was completed at 29-52 ms. The duration of LV endocardial activation was 28-50 ms. This comprised 41% of the total surface QRS complex (mean QRS duration 87 ms, range 80-100 ms).

Wyndham et al. (7) recorded the epicardial ventricular depolarization sequence in 11 patients with normal QRS who were suffering from coronary artery disease and underwent heart surgery. They concluded that their data could be useful as a basis for comparison with the abnormal epicardial activation sequence in ventricular pre-excitation and ventricular tachycardia. Knowledge of the range of normality in epicardial activation sequence could also provide a basis for interpretation of the disordered sequence seen in chronic or surgically induced intraventricular conduction defects.

The heterogeneity and conduction delays described above are relevant to the basis for the QRS dispersion (QRSd) existence, even in the normal heart and in different clinical situations in which the myocardium depolarization is affected. Precordial leads reflect local electrical activity, and thus QRS dispersion is an approximate marker of this in homogeneous depolarization.

QRS dispersion in myocardial infarction patients

Perkiömäki and colleagues studied a set of 100 patients: 30 healthy subjects, 40 patients with a history of myocardial infarction (MI), without arrhythmic events or inducible ventricular tachycardia (VT) at electrophysiological study (EPS), and 30 patients with prior MI and history of cardiac arrest (12 patients) or VT (18 subjects) and inducible monomorphic VT at electrophysiological study (8). Although the focus was QT dispersion (QTd), QRSd was also measured. QRS dispersion was 28 ± 11 ms in the normal group, 46 ± 13 ms in the group with MI and no VT, and 48 ± 16 ms in the group with MI and VT ($p < 0.001$ between patients without VT vs. healthy subjects and between patients with VT vs. healthy subjects). The maximal and minimal QRS duration were also higher in patients with prior MI compared to healthy subjects ($p < 0.001$).

A more extensive study which included 724 patients (9) showed that increased QRS duration (> 110 ms) or dispersion was not correlated with arrhythmic events, and also QRS dispersion was not correlated with death during follow-up.

The effect of therapy of acute MI on QRSd was analyzed mostly indirectly in studies with other main targets. Moreno et al., in a pre-primary PCI era study, analyzed the effect of thrombolysis on QTd and QRSd (10). They included 244 patients with AMI treated with streptokinase or anistreplase. Dispersion of QT, JT, and QRS were measured at 9 ± 5 days after thrombolytic therapy by using a computerized method. The maximal QRS interval was 93 ± 11 ms and was observed in a precordial lead in 56% of patients and from one of the limb leads in 44%. The minimal QRS interval was 68 ± 10 ms and was noticed in a precordial lead in 39% of patients and in limb leads in 61%. The average QRSd was 24 ± 9 milliseconds (range: 6 - 58 ms). QRSd was

not correlated with the perfusion grade observed at coronary angiography (25 ± 10 ms in grade TIMI 0, 22 ± 7 ms in grade TIMI 1, 28 ± 9 ms in grade TIMI 2, and 24 ± 9 ms in grade TIMI 3; p = 0.24).

Mozos studied 16 patients (13 men, 3 women) with prior MI (occurring at least one year prior), searching for correlations between signal-averaged late ventricular potentials (LVP) and 12-lead ECG dispersion indices (QRS, QT and JT intervals) (11). Patients with hypokalemia, hypocalcemia, or hypomagnesaemia and those not in sinus rhythm were excluded. There were 6 patients in class III NYHA heart failure. QRS dispersion was measured manually using at least 8 leads for each patient. The following parameters regarding depolarization were calculated: QRS dispersion (QRSd), QRSdc (heart rate corrected QRSd), QRScmax (heart rate corrected maximum QRS duration) and QRScmin (heart rate corrected minimum QRS duration). The values were compared in two groups of patients: with and without LVP (62.5% had LVP+). The depolarization dispersion parameters had the following values: QRSd = 120 ± 90 ms (110.4 ms in LVP+ vs. 56.8 ms in LVP-, p = 0.05), QRSdc = 32 ± 27 ms (23.8 ms in LVP+ vs. 12.16 ms in LVP-, p = 0.05), QRSmax = 50 ± 30 ms (43.8 ms in LVP+ vs. 30.83 ms in LVP-, p = 0.048), QRSmin 17 ± 11 ms (18.9 ms in LVP+ vs. 18.66 ms in LVP-, p = ns). QRSd correlated with SAECG QRS duration (r = 0.61, Bravais-Pearson) and LAS40 (r = 0.78). QRSdc correlated with SAECG QRS duration (r = 0.48) and LAS40 (r = 0.78). QRSmax correlated with SAECG QRS duration (r = 0.61) and LAS40 (r = 0.72). Other indices had weak correlations. Given the small number of patients, the significance of the results to the larger population remains unclear.

QRD dispersion in heart failure

Anastasiou-Nana et al. followed 104 class II-IV NYHA heart failure patients with systolic dysfunction (left ventricular ejection fraction < 35%) for 20 ± 12 months, with cardiac death as the end-point (12). QRS dispersion was measured using computer software. QRS dispersion was increased in non-survivors (54 ± 17 ms vs. 46 ± 16 ms, p < 0.02). Also, patients with sudden death had significantly higher QRSd compared to survivors (56 ± 13 ms vs. 46 ± 16 ms, p < 0.02). Using a cut-off value of 46 ms for QRSd identified a group with high risk of death in three years (mortality 13% vs. 32%, relative risk 3.85, 95% confidence interval 1.6 to 9.5). The risk was even higher by adding QTd> 90 ms. In a multivariate regression analysis, QRSd was an independent predictor of cardiac death (p = 0.001) and of sudden cardiac death (p = 0.04).

Yamada et al. studied 87 patients with left ventricular ejection fraction (LVEF) less than 40% (measured by magnetic resonance imaging) (13). Cardiac mortality was higher in patients with both abnormal QRSd (> 25 ms) and QTcd (> 62 ms), with better positive predictive value than in those with just one abnormal parameter (63% vs 15%, p = 0.01).

QRS dispersion was incorporated into a prognostic index assessing the long-term mortality of 553 patients with class I-III NYHA heart failure from the UK-HEART study (14). Mean QRSd was 44.6 ± 15.5 ms, median was 42.7 ms, range 12 – 125 ms. In survivors QRSd was 40.6 ms compared with 45.1 ms in non-survivors (geometric means, p = 0.003). QRSd was an independent predictor of all-cause mortality with a hazard ratio of 1.06 (1.02 – 1.1), p = 0.004. The following predictors of mortality were included in the score, with one point each: serum sodium ≥ 140 mmol/l, creatinine ≥ 111 mmol/l, cardiothoracic ratio ≥ 0.52, SDNN ≥ 112 ms, maximum QTc ≥ 487 ms, QRS dispersion ≥ 42.7 ms, the presence of non-sustained VT on 24-hours Holter recordings and LV hypertrophy in 12-lead ECG. In the low-risk group (0–3 points) mortality at 5 years was 20% compared to 53% in the high-risk group (4–8 points). The study was developed

before the era of beta-blockers in heart failure started, so the results need to be confirmed with current standards-of-care. Another point worth mentioning is the need to compare this prognostic score with other well-established easy-to-obtain risk variables, including left ventricular ejection fraction, given the fact that this score included a time-consuming mix of blood tests, imaging, and electrocardiographic techniques.

QRD dispersion in left bundle branch block

Wyndham et al. showed that in patients with left bundle branch block (LBBB), the onset of ventricular epicardial activation is closer to anterior right ventricle than in normal activation, with slow trans-septal activation of LV (7).

Xiao et al. studied the correlation between QRSd and LV function and the asynchrony of ventricular motion in patients with LBBB (15). Forty-two patients with LBBB and 28 normal controls (group C) were included. The LBBB patients were divided into two groups: the isolated LBBB patients (group A, n = 7), and LBBB patients with other organic diseases (group B, n = 35). All the indices were significantly different between group B and group C ($p < 0.05$), except for LVEF. All the indices were significantly different between group A and group B, except for QRS duration. The QRS duration and QRSd were negatively correlated with LV ejection fraction in the two LBBB groups, with the correlation of $r = -0.310$ ($p = 0.046$) for QRS duration and $r = -0.341$ ($p = 0.027$) for QRSd; QRSd and LV systolic asynchrony index (evaluated by echo-cardiography) were positively correlated, with the correlation of $r = 0.318$ ($p = 0.040$).

Is QRS dispersion a potential predictor of response to cardiac resynchronization therapy?

QRS duration and morphology are important criteria for the indication of cardiac resynchronization therapy implantation. In this setting, QRSd was investigated as a possible marker of therapy response. Seventy-six patients with CRT device implant were divided by Qiao and colleagues into three groups: non-responders (n = 23), responders (n = 37) and super-responders (n = 16) (16). Responders met all the following criteria: no cardiovascular death, no heart transplantation, no hospitalization for decompensated heart failure, and improvement of NYHA class. A patient was classified as a super-responder if LVEF was ≥ 50% at follow-up. QRS duration and dispersion were measured on standard 12-lead ECGs at a paper speed of 25 mm/s before and immediately after the implantation. Pre-implant QRSd was 49.5 ± 18.1 ms in non-responders, 43.5 ± 17.0 ms in responders, 38.7 ± 19.2 in super-responders (p = ns). Post-implant QRSd was 40.1 ± 27.9 ms in non-responders, 32.9 ± 21.5 ms in responders, 25.0 ± 15.9 ms in super-responders ($p < 0.05$ compared with non-responders). In a multivariate analysis, none of the variables was independently associated with CRT non-response.

However, other authors found that, unlike QRS maximum duration, QRSd was not a significant predictor of maximum hemodynamic change in patients that have undergone cardiac resynchronization therapy (17).

Dilaveris et al. studied the effects of biventricular pacing on ventricular depolarization and repolarization (by ECG and vectorcardiography) (18). They found QRS duration and dispersion significantly decreased as effect of resynchronization therapy.

Chávez-González et al. selected 19 patients with LBBB, LVEF ≤ 35% and resynchronization therapy (19). QRSd was higher in women (48.0 ± 24.0 ms vs. 37.14 ± 13.8 ms; p=0.04) and decreased after resynchronization, especially in responders. There was a linear correlation between LVEF and QRSd (r=0.34, p=0.02 at six months follow-up). Considering this research, the same group proposes that besides duration, QRS dispersion should be measured in future

investigations about resynchronization therapy, in order to reach better predicting indexes for such electrical therapy (20).

QRS dispersion in cardiomyopathies

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease in which there is a gradual replacement of ventricular myocardium with fibro-fatty tissue, initially predominantly in the right ventricle, with its main feature being the risk of malignant ventricular arrhythmias. The replacement of cardiomyocytes with adipose or fibro-fatty tissue determines the development of viable myocardium islands surrounded by inert areas, with severely altered electrical continuity. The isolated areas are depolarizing significantly later than normal ones and induce QRS duration prolongation in leads facing directly the affected area (i.e., usually V1-V3), with increased QRS dispersion, or if the conduction is even slower, the appearance of a low-amplitude signal at the end of QRS complex (ε - epsilon wave).

To be visible as a separate wave on the surface ECG, this late depolarizing area must have a sufficient size and must depolarize uniformly though later than in the case of a block of one of the His-Purkinje network bundles. The diagnosis of ARVC is established with the 2010 Task Force Criteria, and includes the following types of findings: global and/or regional myocardial dysfunction and structural abnormalities in imaging assessment, histopathology (endomyocardial biopsy), repolarization abnormalities on 12-lead ECG, depolarization abnormalities on 12-lead ECG, arrhythmias, family history and genetics (21). Depolarization abnormalities included are: ε wave in V1–3 (reproducible low-amplitude signals between end of QRS complex to onset of the T wave, major criterion), and signal-averaged ECG with late potentials (if QRS on standard surface ECG < 110 ms, minor criterion) (21).

QRS dispersion has been proposed as a criterion for the diagnosis of ARVC. Turrini and colleagues investigated the value of QRSd as a noninvasive marker of sudden death in 20 sudden death victims with ARVC diagnosed at autopsy (group I), 20 living ARVC patients with sustained VT (group II), 20 living ARVC patients with ≤ 3 consecutive premature ventricular beats (group III), and 20 control subjects (group IV) (22). QRSd was greater in group I compared with group II (45.7 ± 8.1 ms vs. 33.5 ± 8.7 ms, p = 0.0004) and in group II compared with group III (33.5 ± 8.7 ms vs. 28 ± 5.2 ms, p < 0.0001) and group IV (33.5 ± 8.7 ms vs. 18.5 ± 3.6 ms, p < 0.0001). A QRSd ≥ 40 ms had a sensitivity of 90% and a specificity of 77% in identifying patients at risk of sudden death. QRS dispersion was the only independent predictor of sudden death in a multivariate analysis, excepting a history of syncope (odds ratio 1.22, CI 1.11 - 1.35; p < 0.0001) (22).

The value of QRSd as an independent predictor of sudden death in ARVC has been confirmed in other studies. Nasir and co-workers analyzed a number of ECG characteristics in 50 patients with ARVC, 50 matched controls, and 28 patients with right ventricular outflow tract tachycardia (23). QRSd ≥ 40 ms was present in 44% of patients with ARVC without right bundle branch block (RBBB) vs. 4% in right ventricular outflow tract (RVOT) tachycardia group (p < 0.0001) vs. 0% in normal controls (p < 0.0001). The presence of RBBB had no influence on dispersion. In patients without RBBB the only significant predictors of inducibility of VT at EPS after logistic regression analysis were prolonged S-wave upstroke in V1 through V3 ≥ 70 ms (odds ratio 7.2; 95% CI 1.2 - 43.8; p = 0.03) and QRS dispersion ≥ 40 ms (odds ratio 6.1; 95% CI 1.0 - 37.6; P = 0.05). It has been reported that a QRS dispersion ≥ 50 ms was a predictor of recurrent arrhythmic events in a cohort of 121 consecutive patients (24). Hulot et al. confirmed the value of QRS dispersion

as a risk factor for cardiovascular death in a cohort of 130 patients (100 men; age at onset of symptoms, 31.8 ± 14.4 years) followed-up 8.1 ± 7.8 years (25). QRS dispersion > 40 ms was recorded in 40% of the patients and was significantly more frequent in the group with cardiovascular death compared with the group of survivors or with non-cardiovascular death (57.1% vs. 36.7%, p = 0.08). QRS dispersion > 40 ms was a predictor of cardiovascular death (OR = 2.30, 0.89 - 5.95, p = 0.08) comparable with recurrence of ventricular tachycardia. The best predictor was the presence of right heart failure (odds ratio = 10.99) (25).

Electrocardiographic abnormalities in ARVC, including QRS dispersion, are dynamic features of ARVC, as was demonstrated in a study on 317 ECGs from 68 genotyped patients (34 with disease-causing mutations) during follow-up of 34 ± 28 months (26). In this cohort, 23% of patients had new or dynamic ECG changes. ECG changes present at baseline were: T wave inversion beyond V2 (39.7%), epsilon waves (5.9%), localized prolongation of the QRS complex in V1-V3 (14.7%), and QRS dispersion ≥ 40 ms (10.3%). QRS dispersion was relatively stable during follow-up with no significant changes in 89.7% without QRSd at baseline and 8.8% of patients with QRSd at baseline. Very interestingly, in one patient QRSd was present at baseline but normalized during follow-up, due to QRS prolongation in left precordial leads, supposedly through left ventricular involvement. This evolution of QRSd is consistent with the hypothesis of a correlation between electrocardiographic dispersion and structural changes in the myocardium, but also suggests that in more advanced disease states with bi-ventricular involvement, QRSd may lose sensitivity (26).

Cardiac magnetic resonance (CMR) imaging is an important tool for diagnosis of ARVC. A study by Ma and colleagues assessed the correlations between the presence of right ventricular abnormalities detected by CMR and QRS dispersion in 40 consecutive patients (27). Using the cut-off value of 40 ms for QRSd separated the patients in two groups with significant structural differences. Patients with QRSd ≥ 40 ms had higher dimensions of right ventricle function: end-diastolic diameter (57 ± 10 mm vs. 48 ± 11 mm, p = 0.012), end-systolic diameter (52 ± 10 mm vs. 44 ± 11 mm, p = 0.010), end-diastolic volume (260 ± 105 ml vs. 180 ± 66 ml, p = 0.006), end-systolic volume (222 ± 98 ml vs. 148 ± 61 ml, p = 0.006) and higher myocardial fibrosis detection rate (74% vs. 38%, p = 0.024). Analyzing the group as a whole, QRS dispersion correlated significantly with right ventricular end-diastolic volume (r = 0.66, p < 0.001), right ventricular end-systolic volume (r = 0.67, p < 0.001), right ventricular outflow tract area (r = 0.68, p < 0.001) (27).

Hypertrophic cardiomyopathy is another arrhythmogenic disease in which simple, specific and sensitive ECG risk markers are needed. QRS dispersion was tested, but only indirectly and in a small number of patients. Sakata et al., in a retrospective analysis of echocardiography and electrocardiography in 70 patients with hypertrophic cardiomyopathy, did not find a correlation between QRS duration or dispersion and the distribution of LV hypertrophy (28). The relationship with wall thickness was not tested. Kawasaki et al. enrolled 70 patients with hypertrophic cardiomyopathy and anteroseptal wall hypertrophy, 8 patients with lateral wall hypertrophy, 8 patients with diffuse hypertrophy, and 46 normal controls (29). Standard 12-lead ECG parameters were analyzed. QRS dispersion was highest in the group with anteroseptal hypertrophy (43.0 ± 10.6 ms), followed by the group with lateral wall hypertrophy (32.9 ± 11.9 ms). In these patients, there was a superposition of localization of QRS increased duration with the echocardiographic disposition of hypertrophy. The group with diffuse hypertrophy was not different from controls. QRS dispersion was not significantly

different in patients with or without markers of risk (syncope, ventricular tachycardia, cardiac events), or between patients of different NYHA functional class (29).

Conclusions

As a conclusion, the QRS dispersion is a simple electrocardiographic marker with potential value in the assessment of patients in different clinical settings: ischemic heart disease, heart failure, and cardiomyopathies. More studies are needed to validate its clinical utility for predicting the risk for ventricular arrhythmias and sudden cardiac death, and for the evaluation of the response to cardiac resynchronization therapy.

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