Dispersion of Ventricular Depolarization-Repolarization
A Noninvasive Marker for Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy

Pietro Turrini, MD, PhD; Domenico Corrado, MD; Cristina Basso, MD, PhD; Andrea Nava, MD; Barbara Bauce, MD; Gaetano Thiene, MD

Background—We retrospectively investigated the value of clinical and ECG findings as well as QT-QRS dispersion in predicting the risk of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Methods and Results—Duration and interlead variability of the QT interval and QRS complex were measured manually from standard ECGs in 20 sudden death victims with ARVC diagnosed at autopsy (group I), in 20 living ARVC patients with sustained ventricular tachycardia (group II), in 20 living ARVC patients with ≥3 consecutive premature ventricular beats (group III), and in 20 control subjects (group IV). QT and QRS dispersions were greater in group I (77.5±10.6 ms for QT and 45.7±8.1 ms for QRS) compared with group II (64.5±13.9 ms for QT [P=0.001] and 33.5±8.7 ms for QRS [P=0.0004]) and in group II compared with group III (48±8.9 ms for QT [P<0.0001] and 28±5.2 ms for QRS [P<0.0001]) and group IV (33.5±4.8 ms for QT [P<0.0001] and 18.5±3.6 ms for QRS [P<0.0001]). Negative T wave beyond V1 and syncope were statistically more frequent in group I (P=0.02 and P=0.007, respectively). On multivariate analysis, QRS dispersion remained an independent predictor of sudden death (P<0.0001), followed by syncope (P=0.09). In assessing risk of sudden death, QRS dispersion ≥40 ms had a sensitivity and specificity of 90% and 77%, respectively; QT dispersion >65 ms, 85% and 75%, respectively; negative T wave beyond V1, 85% and 42%, respectively; and syncope, 40% and 90%, respectively.

Conclusions—QRS dispersion (≥40 ms) was the strongest independent predictor of sudden death in ARVC. Syncope, QT dispersion >65 ms, and negative T wave beyond V1, refined arrhythmic risk stratification in these patients. (Circulation. 2001;103:3075-3080.)

Key Words: cardiomyopathy ■ death, sudden ■ electrocardiography
Methods

Patient Population

We examined 12-lead ECGs in 4 different groups of patients, for whom Table 1 gives the main clinical and ECG data. Group I included 20 consecutive patients with ARVC and available ECG who died suddenly. The pathological diagnosis was proven at autopsy in all and was based on the finding of gross and/or histological evidence of transmural loss of myocardium with fibrofatty replacement of the RV free wall myocardium, either regional or diffuse, in the absence of valve, coronary, and pericardial disease or other known cardiac or noncardiac causes of death.3,6 Groups II and III included 20 age- and sex-matched living patients, each with an overt form of ARVC. All the patients fulfilled the diagnostic criteria of ARVC recommended by the Task Force of the European Society of Cardiology.17 According to these criteria, ARVC was defined to be diffuse when imaging techniques such as echocardiography, angiography, MRI, or radionuclide scintigraphy showed a widespread RV involvement with global RV dilatation and ejection fraction reduction. Localized RV disease was diagnosed in the presence of regional RV lesions, such as segmental RV wall motion abnormalities (hypo-akinetic or dyskinetic areas), with mild or no ejection fraction reduction. At postmortem examination, RV involvement was defined according to Fontaine et al18 as distinct waves of small amplitude that occupy the QT segment in the right precordial leads; ST-segment elevation, defined as high take-off ST-segment elevation ≥1 mm of “coved” or “saddle-back” type were excluded.

ECG Measurements

No patients were on antiarrhythmic drugs or other drugs known to affect the QRS complex and/or the QT interval during or before acquisition of the ECG tracings analyzed in the present study. All patients were in sinus rhythm. The 12-lead ECGs were obtained in the traditional lead position and recorded at 25 mm/s. To increase the accuracy of measurements, all the ECGs were enlarged 2 to 3 times.

TABLE 1. Comparison of Clinical and ECG Data in the 4 Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, y</th>
<th>Sex (male/female), n</th>
<th>RR interval, ms</th>
<th>Isolated complete RBBB, n (%)</th>
<th>Isolated ST-segment elevation on right precordial leads, n (%)</th>
<th>Complete RBBB and ST-segment elevation on right precordial leads, n (%)</th>
<th>e wave, n (%)</th>
<th>Negative T-wave beyond V1, n (%)</th>
<th>Syncope, n (%)</th>
<th>Left ventricular involvement, n (%)</th>
<th>Diffuse RV involvement, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24.8±6.5</td>
<td>17/3</td>
<td>975±136</td>
<td>3 (15)</td>
<td>7 (35)</td>
<td>1 (5)</td>
<td>7 (35)</td>
<td>17 (85)†</td>
<td>8 (40)‡</td>
<td>7 (35)‡</td>
<td>16 (80)‡</td>
</tr>
<tr>
<td>II</td>
<td>26.4±6.2</td>
<td>18/2</td>
<td>982±117</td>
<td>3 (15)</td>
<td>8 (40)</td>
<td>0</td>
<td>5 (25)</td>
<td>14 (70)</td>
<td>4 (20)</td>
<td>6 (30)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>III</td>
<td>22.4±7.4</td>
<td>16/4</td>
<td>943±117</td>
<td>1 (5)</td>
<td>3 (15)</td>
<td>0</td>
<td>6 (30)</td>
<td>9 (45)</td>
<td>0</td>
<td>6 (30)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>IV</td>
<td>25.9±5.4</td>
<td>16/4</td>
<td>935±139</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pts indicates patients. Values are mean±1 SD or number (percentage). *P<0.02 vs groups II and III; †P<0.007 vs groups II and III.

PTs indicates patients. Values are mean±1 SD or number (percentage).

In all and was based on the finding of gross and/or histological evidence of transmural loss of myocardium with fibrofatty replacement of the RV free wall myocardium, either regional or diffuse, in the absence of valve, coronary, and pericardial disease or other known cardiac or noncardiac causes of death.3,6 Groups II and III included 20 age- and sex-matched living patients, each with an overt form of ARVC. All the patients fulfilled the diagnostic criteria of ARVC recommended by the Task Force of the European Society of Cardiology.17 According to these criteria, ARVC was defined to be diffuse when imaging techniques such as echocardiography, angiography, MRI, or radionuclide scintigraphy showed a widespread RV involvement with a global RV dilatation and ejection fraction reduction. Localized RV disease was diagnosed in the presence of regional RV lesions, such as segmental RV wall motion abnormalities (hypo-akinetic or dyskinetic areas), with mild or no ejection fraction reduction. At postmortem examination, RV involvement was defined according to Fontaine et al18 as distinct waves of small amplitude that occupy the QT segment in the right precordial leads; ST-segment elevation, defined as high take-off ST-segment elevation ≥1 mm of “coved” or “saddle-back” type were excluded.

ECG Measurements

No patients were on antiarrhythmic drugs or other drugs known to affect the QRS complex and/or the QT interval during or before acquisition of the ECG tracings analyzed in the present study. All patients were in sinus rhythm. The 12-lead ECGs were obtained in the traditional lead position and recorded at 25 mm/s. To increase the accuracy of measurements, all the ECGs were enlarged 2 to 3 times. The QT interval and QRS-complex duration were measured manually at each lead by means of a method previously described.20,21 The QT interval was measured from the onset of the QRS complex to the end of the T wave, ie, return to the T-P baseline. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. The QRS-complex duration was measured from the beginning of the QRS complex to its end. When the offset of QRS complex was difficult to define because of a gradual slope toward a plateau, it was measured at the intersection of the S wave with the isoelectric baseline. The JT interval was calculated by subtracting QRS duration from QT (means) interval in individual leads. When ever possible, 3 consecutive cycles were measured in each of 12 leads to calculate a mean value of RR from these 3 values. When the end of the QRS complex or T wave could not be identified, the lead was not included. Three precordial leads at least and a minimum of 7 leads were required for QT/QRS/JT dispersion. The QT, QRS, and JT dispersions were defined as the difference between the maximum and minimum QT, QRS, and JT values occurring in any of the 12 ECG leads, respectively.

The percentage of missing leads for determination of QT dispersion and QRS dispersion was 8.7% and 4.2%, respectively, for group I; 9.2% and 5%, respectively, for group II; 7.9% and 4.6%, respectively, for group III; and 6.2% and 2%, respectively, for group IV.

Cutoff values and correlations between dispersions of QT, QRS, and JT intervals were assessed by using uncorrected values. In addition, we provide rate-corrected values of QT and JT intervals and dispersions with the use of Bazett’s formula.

Two independent observers, blinded as to the clinical data, tested the repeatability of these measurements in a random sample of 20 ECGs. For the same ECG tracings, the percentage differences in QT/QRS/JT dispersion measurements ranged from 2% to 6% for...
Results

Statistical Analysis

All analyses were performed with STATA, version 6.0 (STATA Corp, 1999). All continuous variable values are reported as mean ± SD. Continuous variables were analyzed by use of ANOVA with the Bonferroni correction for multiple comparisons or by use of the Spearman correlation of ranks when appropriate. Categorical variables were analyzed by use of contingency tables and the Pearson chi-squared method. The independent correlation of clinico-ECG variables with sudden death was determined by means of multivariate logistic regression analysis, with sudden death as a dependent variable. Variables with a value of \( P \leq 0.1 \) in the univariate analysis (maximum QT interval [both uncorrected and rate-corrected] and QRS complex, QT/QRS/JT dispersion, rate-corrected QT and JT dispersions, negative T wave beyond V1, syncpe, ST-segment elevation in right precordial leads, and RBBB) were considered candidates for multivariable analysis. We estimated the odds ratio and 95% CIs of the variables independently associated with sudden death. A value \( P \leq 0.05 \) was considered statistically significant.

Clinical and ECG Findings

History of syncope was statistically more frequent in group I than in groups II and III (Table 1). RR intervals were similar in the 4 groups. The incidence of negative T wave beyond V1 was higher in group I than in groups II and III. Only 1 patient of group I showed complete RBBB with coexistent ST-segment elevation.

QT/QRS/JT Interval

Table 2 reports maximum and minimum QT, QRS, and JT intervals in the 4 groups. QT and QRS intervals tended to be higher in group I. Maximum values of QRS and QT intervals were measured in the right precordial leads in all the patients of groups I, II, and III. In group IV, maximum QT interval and QRS duration were found in the right precordial leads in 10 and 8 subjects, respectively.

QT/QRS/JT Dispersion

QT and QRS dispersions (Table 3) were greater in group I than in group II and greater in group II than in groups III and IV. JT dispersion did not differ significantly in the 3 ARVC groups. In group I, the subgroup of 4 patients with RBBB had similar values of QT, QRS, and JT dispersions compared with the subgroup of patients without RBBB (with RBBB versus without RBBB, respectively: 81.2 ± 8.6 vs. 76.8 ± 11.9 ms [\( P = NS \) for QT, 50.8 ± 3.6 vs. 44.6 ± 8 ms [\( P = NS \) for QRS, and 35.2 ± 5.7 vs. 32.8 ± 4.4 ms [\( P = NS \) for JT]). Also, in group II, the subgroup of 3 patients with RBBB had similar values of QT, QRS, and JT dispersions compared with the subgroup of patients without RBBB (with RBBB versus without RBBB, respectively: 73.3 ± 11.5 versus 62.9 ± 14 ms [\( P = NS \) for QT, 43.3 ± 11.5 versus 31.1 ± 7.2 ms [\( P = NS \) for QRS, and 33.3 ± 5.7 versus 32.3 ± 8.3 ms [\( P = NS \) for JT]).
Figures 1 and 2 provide the individual values of QT and QRS dispersions, respectively, in the 3 ARVC groups.

Correlations Between Intervals and Dispersions
There were significant correlations between QRS duration or QT interval and the dispersions of QT/QRS/JT when all the ARVC patients were considered as a single group (Table 4). QT dispersion correlated strongly with QRS dispersion and JT dispersion. There was a particularly close correlation between QRS dispersion and maximal QRS duration. QT dispersion had a significant relationship with maximum QT interval.

Accuracy of Clinico-ECG Variables in Predicting the Risk of Sudden Death
A history of syncope had a sensitivity and specificity in predicting the occurrence of sudden death of 40% and 90%, respectively; a negative T wave beyond V1 had a sensitivity and specificity in predicting the occurrence of sudden death of 85% and 42%, respectively.

For QT, QRS, and JT dispersions, we considered as the upper limit of low arrhythmic risk the 99% tolerance limits (mean ±2 SD) of the values of group III. The following cutoff values were indicative of high risk: QT dispersion >65 ms, QRS dispersion ≥40 ms, and JT dispersion ≥40 ms.

A QRS dispersion ≥40 ms showed a sensitivity and a specificity in identifying patients at risk of sudden death of 90% and 77%, respectively (Figure 2); a QT dispersion >65 ms, 85% and 75%, respectively (Figure 1); and a JT ≥40 ms, 30% and 72%, respectively. When these parameters were used in combination, there was an increased in specificity for QRS plus QT dispersion (82%) and for QT plus QRS plus JT dispersions (85%) associated with a reduction of sensitivity (85% and 30%, respectively).

Multivariate Analysis of Risk Factors for Sudden Death
We performed a stepwise logistic regression analysis incorporating all the clinical and ECG-derived variables to determine independent predictors of sudden death. Only QRS dispersion remained an independent predictor of sudden death (odds ratio 1.22, CI 1.11 to 1.35; P<0.0001), followed by history of syncope (odds ratio 5.9, CI 0.71 to 49.44; P=0.09).

Discussion
The main findings of the present study were that QRS dispersion (≥40 ms) was the strongest independent predictor of sudden death in ARVC patients; increased QRS dispersion resulted mainly from localized prolongation of the QRS complex in the right precordial leads; syncope, QT dispersion >65 ms, and negative T wave beyond V1 refined noninvasive risk stratification for sudden death.

Pathophysiology of Ventricular Arrhythmias in ARVC
VT and fibrillation are well-documented causes of sudden death in ARVC.1,2,4,8 The peculiar histopathology of the disease predisposes the patient to malignant ventricular arrhythmias.18,22 In ARVC, VT is generally believed to be reentrant4,9 and is usually accompanied by abnormalities of ventricular activation.4,23 Localized prolongation of QRS duration in the right precordial leads is a well-recognized feature of ARVC, and a duration of ≥110 ms is considered a main diagnostic criterion.17 A reentry mechanism is suggested by the inducibility of VT by programmed ventricular stimulation,4,18,22 together with a high frequency of late potentials,24,25 and by the finding of areas of slow conduction during endocardial mapping of the RV.4,26,27 Recently, it has been hypothesized that repolarization abnormalities in ARVC may facilitate the occurrence of ventricular arrhythmias with a mechanism that can be modulated by autonomic nervous system activity.24

QT Dispersion
Experimental studies have provided powerful evidence that nonuniform recovery of ventricular excitability plays an important role in the mechanism of ventricular arrhythmias.28 Potentially arrhythmogenic nonuniform recovery of excitability is the result of either dispersion of refractoriness or activation times depending on the underlying pathophysiological substrate.29 The interlead variability in QT-interval duration on the standard 12-lead ECG, the so-called QT dispersion, is a noninvasive method for detecting regional differences in ventricular recovery time.13 Experimental studies confirmed that QT dispersion is significantly correlated with dispersion of ventricular recovery time, measured directly from myocardium.30 The studies on QT dispersion have
provided information about regional variations in ventricular repolarization in many diseases characterized by malignant ventricular arrhythmias, such as myocardial infarction, coronary artery disease, long-QT syndrome, hypertrophic cardiomyopathy, chronic heart failure, and repaired tetralogy of Fallot.

In our ARVC patient population, QT dispersion was significantly greater in the patients who died suddenly compared with living patients with different arrhythmic profiles. Our cutoff value for QT dispersion, >65 ms, is similar to that reported by Surawicz. Also, Benn et al measured an increased QT dispersion in ARVC patients, but they did not find significant differences between individuals considered at low and high risk for life-threatening arrhythmias. However, patients who died suddenly were only 5 of 11 high-risk patients (45%), and the mean QRS duration of the whole high-risk group was smaller than that of our victims of sudden death. Peeters et al, analyzing ARVC patients with sustained VT and overt forms of the disease, did not find an increased QT dispersion, although they demonstrated that repolarization abnormalities were present at body surface mapping and might have been related to the occurrence of ventricular arrhythmias. A smaller mean QRS duration and a lower number of patients could explain the discrepancy with the present findings.

It has been recently advanced that QT dispersion may be an index of general repolarization abnormalities instead of an expression of regional heterogeneity of myocardial refractoriness. Accordingly, T-wave loop dynamics and the variable projections of the loop into individual ECG leads has been proposed to be the true mechanistic background of QT dispersion. This concept was in keeping with our finding that in victims of sudden death, a negative T wave beyond V1, as “any potential in V1-V3 exceeding the QRS duration in lead V6 by more than 25 ms” and regarded as a diagnostic marker for ARVC. The present study further demonstrated that increased QT dispersion is the strongest independent predictor of sudden death. A cutoff value ≥40 ms had a good sensitivity and specificity in predicting the occurrence of sudden death. Also, Peters et al demonstrated that increased QT dispersion ≥50 ms was a strong predictive factor of recurrent malignant arrhythmic events.

Two mechanisms leading to sudden death in ARVC have been proposed by Fontaine et al, ie, depolarization abnormalities mediated by a sympathetic mechanism and repolarization abnormalities facilitated by parasympathetic drive. Our data confirm that both depolarization and repolarization abnormalities do exist in patients at risk for sudden death. However, depolarization abnormalities are most commonly associated with cardiac arrest.

**Study Limitations**

This is a retrospective study that was carried out in a young population of ARVC patients with comparable clinical characteristics. Therefore, the ability to transfer our results to ARVC patients older or with different clinical picture remains to be elucidated. The correlation between ECG parameters and the risk of sudden death may change with age, extent, and progression of ARVC and severity of left ventricular involvement, all variables that may have a significant and independent influence on the proposed ECG parameters and may affect the correlation with sudden death risk.

The present study investigated the ECG features of ARVC patients, either living or experiencing sudden death, before starting antiarrhythmic drug therapy. The subsequent follow-up of these patients on antiarrhythmic drug treatment or after implantation of cardioverter defibrillator was not addressed. Whether pharmacological or nonpharmacological therapy modifies ARVC natural history by preventing sudden death cannot be derived from the present data and needs to be evaluated by prospective studies.
Conclusions
This was the first study to address the prognostic value of clinical and ECG variables in ARVC patients who died suddenly compared with living patients with different degrees of arrhythmic risk. Our data indicate that QRS dispersion (≥40 ms) is the strongest independent predictive marker of sudden death in ARVC patients and that syncope as well as QT dispersion (≥65 ms) and negative T wave beyond V1 refine noninvasive arrhythmic risk stratification. Because maximum QRS complex and QT interval were found in the right precordial leads, these leads appear to be crucial in the diagnosis and risk stratification of ARVC.

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References
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