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

The natural history of arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) is a function of both the electrical instability of dystrophic myocardium, which can precipitate sudden death any time during the disease course, and the progressive myocardial loss that results in ventricular dysfunction and heart failure.1-5 Sudden death accounts for the majority of the fatal events, and it is more common in adolescents and young adults.6 Invasive markers for unfavorable outcome in ARVC include inducible ventricular tachycardia (VT), drug failure during serial electrophysiological studies, RV dilatation, and left ventricular involvement.7,8 In contrast, there is still limited clinical information on noninvasive risk stratification, especially when no sustained VT has been documented.9 Patients with a history of syncope,10,11 familial sudden death,12 and precordial T-wave inversion beyond V1,8 seem to have a worse prognosis.

Measurement of the interlead variability in QT-interval duration on the standard 12-lead ECG, known as QT dispersion, has been proposed as a simple noninvasive method for detecting regional differences in ventricular recovery times of excitability.13 In ARVC, body-surface QRST integral mapping revealed the presence of repolarization abnormalities,14 which might be correlated with vulnerability to malignant ventricular arrhythmias.15 Benn et al16 measured an increased QT dispersion in ARVC patients, without significant differences between individuals considered at low and high risk for life-threatening arrhythmias. Peters et al8 demonstrated that an increased dispersion of QRS complex in precordial leads was a noninvasive predictor of recurrent arrhythmic events. However, these ECG markers have never been evaluated in patients who died suddenly with ARVC proven at autopsy.

The present study was designed to investigate the value of clinical and ECG findings as well as QT-QRS dispersion in predicting the risk of sudden death in a large group of ARVC patients.
TABLE 1. Comparison of Clinical and ECG Data in the 4 Groups

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

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.1,3-6 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 as diffuse or regional when fibrofatty replacement of the RV was found to be widespread or segmental, respectively. Left ventricular involvement was diagnosed in the presence of either localized or diffuse pathological lesions/wall motion abnormalities of the left ventricular free wall, with or without septal involvement. Endomyocardial biopsy was available for all patients from group II and for 14 of 20 patients from group III. The extent of RV disease and incidence of left ventricular involvement were comparable in the 3 ARVC groups (Table 1). Patients of group II experienced spontaneous sustained (>30-second) monomorphic VT (mean rate 210±37 bpm), whereas patients of group III had ≤3 consecutive premature ventricular beats at ECG and/or Holter monitoring. Group IV consisted of 20 age- and sex-matched healthy control subjects with no history of arrhythmia or syncope and normal ECG patterns.

ECG Features
Analysis of ECG focused on the following parameters: e waves, defined according to Fontaine et al19 as distinct waves of small amplitude that occupy the QT segment in the right precordial leads; negative T wave beyond V1; ST-segment elevation, defined as maximal displacement of ST segment with upward convexity ≥0.5 mm from the isoelectric line; and complete right bundle-branch block (RBBB), defined as a prolonged QRS complex ≥120 ms. Patients with a Brugada-like ECG pattern (Brugada and Brugada14) characterized by 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 obtain for all a format comparable to 50 mm/s. 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. Whenever 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
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within-observer variability and 2% to 7% for between-observer variability.

Statistical Analysis
All analyses were performed with STATA, version 6.0 (STATA Corp, 1999). All continuous variable values are reported as mean ± 1 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 χ² 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. A value of 0.05 was considered statistically significant.

Results
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.

There was no significant difference in e waves as well as ST-segment elevation among the ARVC groups. Isolated complete RBBB was found in 3 patients each in groups I and II and in 1 patient in group 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 QT 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 values in the subgroup of patients without RBBB (with RBBB versus without RBBB, respectively: 81.2 ± 8.7 versus 73.3 ± 5.7 ms [P = NS] for QT, 50.8 ± 8.6 versus 44.6 ± 5.7 ms [P = NS] for QRS, and 35.2 ± 7.2 versus 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).

| Table 2. Comparison of QT/QRS/JT Interval in the 4 Groups |
|------------------|------------------|------------------|------------------|------------------|
| Group I (20 Pts) | Group II (20 Pts) | Group III (20 Pts) | Group IV (20 Pts) |
| QT, ms           | 445 ± 30.7       | 433 ± 36.5       | 410 ± 30.7       | 387.5 ± 25.7     |
| QTc, ms          | 367 ± 31.3       | 366 ± 30.2       | 362 ± 29.8       | 354 ± 24.5       |
| JT, ms           | 453 ± 16.5       | 436.9 ± 20       | 422.9 ± 20       | 402.5 ± 16.4     |
| QTc, ms          | 374 ± 18.3       | 371.4 ± 20.2     | 373.2 ± 20.6     | 366.5 ± 18.1     |
| QRS, ms          | 125 ± 16.3       | 113 ± 21         | 106.5 ± 9.8      | 88 ± 8.9         |
| JT, ms           | 79.5 ± 15.7      | 78.7 ± 14.6      | 78.5 ± 8.7       | 69.6 ± 9.4       |
| JT, ms           | 320.7 ± 28.1     | 319 ± 34.1       | 307 ± 26.9       | 300 ± 19.1       |

*Group I vs group II; †Group II vs group III; ‡group II vs group IV.

| Table 3. Comparison of QT/QRS/JT Dispersion in the 4 Groups |
|------------------|------------------|------------------|------------------|------------------|
| Group I (20 Pts) | Group II (20 Pts) | Group III (20 Pts) | Group IV (20 Pts) |
| QTD, ms          | 77.5 ± 10.6      | 64.5 ± 13.9      | 48 ± 8.9         | 33.5 ± 4.8       |
| QTDc, ms         | 78.5 ± 10.4      | 65 ± 12.4        | 49.6 ± 8.6       | 34.8 ± 4.4       |
| QRSd, ms         | 45.7 ± 8.1       | 33.5 ± 8.7       | 28 ± 5.2         | 18.5 ± 3.6       |
| JTd, ms          | 33.2 ± 4.6       | 32.5 ± 7.8       | 27.5 ± 6.3       | 21 ± 5.5         |
| JTDc, ms         | 34.5 ± 4.6       | 31.7 ± 7.9       | 29.3 ± 6.7       | 21.7 ± 5.3       |

QTD indicates QT dispersion; QTDc, rate-corrected QTd; QRSd, QRS dispersion; JTd, JT dispersion; and JTDc, rate-corrected JTd.

*Group I vs group II; †group II vs group III; ‡group II vs group IV.
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 arrhythmias15 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
TABLE 4. Correlations in Total Patients With ARVC

<table>
<thead>
<tr>
<th></th>
<th>QT Max</th>
<th>QRS Max</th>
<th>QRSD</th>
<th>QTD</th>
<th>JTD</th>
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</table>

Abbreviations as in Table 3.

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 V6, which is another marker of repolarization abnormalities, showed approximately the same sensitivity of QT dispersion but less specificity.

QRS Dispersion

Because QT dispersion has been taken to represent regional inhomogeneity of repolarization times, QRS dispersion is likely to represent regional inhomogeneity of depolarization times, as a consequence of a ventricular conduction defect. QRS dispersion was closely correlated with maximal QRS duration in total patients with ARVC. This finding suggests the major role of localized prolongation of QRS complex in determining the increased QRS dispersion. Such an increased QRS dispersion has many parallels with the revisited definition of ε waves, which are now considered by Fontaine et al 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 an increased QRS 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 QRS 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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