QT-Interval Prolongation in Right Precordial Leads: An Additional Electrocardiographic Hallmark of Brugada Syndrome

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OBJECTIVES
The aim of this study was to evaluate whether the occurrence of the Brugada Syndrome typical electrocardiogram (ECG) pattern (i.e., right bundle branch block, coved-type ST-segment elevation, and T-wave inversion in the right precordial leads) is characterized by a concomitant lengthening of QT intervals in the right precordial leads.

BACKGROUND
It has been suggested that the typical ECG pattern of Brugada syndrome is due to a decreased net inward current during phase 1 of the action potential, which also leads to its prolongation in the right epicardium.

METHODS
Thirty-two subjects (19 males) age 37 ± 15 years with a suspicious baseline ECG, or who were relatives of Brugada syndrome patients, underwent 12-lead ECG before and after the administration of flecainide.

RESULTS
The flecainide test was negative in 14 and positive in 18 subjects. After flecainide administration, the positive ECGs were characterized by a greater QT interval corrected for heart rate (QTc) prolongation in the right precordial leads than that in the negative ECGs (78.2 ± 35.5 ms vs. 22.0 ± 28.4 ms in V1 and 107.1 ± 43.8 ms vs. 26.7 ± 30.1 ms in V2; p < 0.01), whereas there was no difference in the QTc prolongation in the left precordial leads (55.2 ± 25.3 ms vs. 35.1 ± 28.1 ms in V5 and 53.1 ± 32.8 ms vs. 27.3 ± 22.4 ms in V6; p = NS).

CONCLUSIONS
In accordance with the electrophysiological background, the typical ECG pattern of Brugada syndrome is also characterized by a considerable prolongation of the QT interval in right precordial leads. (J Am Coll Cardiol 2003;42:1632–7) © 2003 by the American College of Cardiology Foundation

Brugada syndrome is an inherited clinical entity characterized by a high risk of sudden cardiac death, by distinct spontaneous or sodium channel blocker-induced electrocardiographic (ECG) findings of right bundle branch block, ST-segment elevation, and inverted T wave in the right precordial leads. (1–3). It has been suggested that the underlying mechanism may be a decreased net inward current or increased net outward current during phase 1 of the action potential (AP) (3,4) and that the resulting ionic abnormalities may be responsible for an increase in the magnitude of the right epicardial AP notch (i.e., stronger repolarization leading to more negative potential at the nadir of the notch). This could lead to a reduced availability of calcium current, resulting in a delay in the emergence of the second upstroke and in the onset of phase 3 and, at least, in a prolongation of the AP itself (3).

The aim of this study was to evaluate whether the occurrence of the typical Brugada syndrome ECG pattern is characterized by a concomitant lengthening of QT intervals in the right precordial leads.

METHODS
Study population. Thirty-two of 35 subjects referred to our Institution for a Brugada syndrome diagnostic work-up (19 males; mean age, 37 ± 15 years) with a negative or suspect ECG underwent a flecainide test; the remaining three had typical baseline ECGs and were excluded. There were 11 probands: one had a history of cardiac arrest, three a history of syncope, and seven were identified during routine examinations. The other 21 subjects (all asymptomatic) were recruited during family screenings after the diagnosis of Brugada syndrome in a family member. Structural heart disease was ruled out by means of non-invasive methods (echocardiography and nuclear magnetic resonance), and 13 patients also underwent coronary angiography, left and right ventriculography, and biopsy. The study was approved by our local ethics committee, and all of the subjects gave their informed consent to participate.

Flecainide test protocol. The evaluations were made in the morning in a quiet and light-attenuated room. The subjects were asked to remain resting in a supine position throughout the procedure. Flecainide was intravenously infused (2 mg/kg body weight over 10 min), and the subjects were continuously monitored until 30 min after the completion of drug administration using a conventional bedside monitor (Hewlett Packard model 78354C, An-
dover, Massachusetts). A simultaneous 12-lead ECG (Hewlett Packard model M1702A) was recorded at a paper speed of 25 mm/s and an amplitude of 10 mm/mV under baseline conditions and 5 min after the end of flecainide administration, when the effect of the drug reaches steady state (5). The ECGs were considered typical when they had a coved-type pattern: a terminal r' wave with a J-point elevation of ≥2 mm and a slowly descending ST segment in continuation with a flat or negative T wave in leads V1 to V2 (6). A saddle-type pattern was not considered typical (6). Typical flecainide-induced ECGs were used to classify the subjects into positive and negative groups (Fig. 1).

**ECG analysis.** The 12-lead ECGs were scanned by a flat scanner (HP ScanJet 5300C, Hewlett Packard) with a resolution of 600 dots per inch (equivalent to 1 m per dot) and then displayed on a monitor. The QRS duration, QT interval, and the preceding RR interval were measured using specific software written in Visual Basic 6.0 language for PC-compatible computers that works with all Windows operating systems. The software provided the use of semi-automatic calculation. The ECGs were analyzed by a single operator and validated by another. As an accurate estimate of precordial QRS is difficult to obtain in Brugada patients, its duration was calculated in standard leads from the start to the end of the QRS complex, and the longest QRS was considered (7). The QT interval and the QT interval corrected for heart rate (QTc, Bazett's formula) were calculated in V1 to V6 (8). The QT interval was calculated from the onset of the QRS complex to the end of the T wave, at the point in which it returned to the isoelectric line (9). Leads with a small T wave (<50 μV) were excluded (10). A detectable deflection after the T wave was considered a U wave when the interval between the end of the T wave and the apex of the doubtful deflection was ≥100 ms (11). The inter- and intraobserver reproducibilities of the RR interval, QRS duration, and the QT interval in V1 to V6 were almost perfect (Intraclass Correlation Coefficient >0.97) (12).

**Molecular analysis.** All screened subjects underwent molecular genetic analysis. All 28 exons of the SCN5A gene were amplified by means of polymerase chain reaction (PCR) using intronic primers from genomic DNA isolated from the peripheral leukocytes of all of the subjects. The PCR products underwent single-strand conformation polymorphism (SSCP) analysis using precast polyacrylamide gels (Amersham Pharmacia, Biotech, Uppsala, Sweden), followed by the direct sequence analysis of aberrant con-

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**Figure 1.** Right and left precordial leads at baseline and after flecainide administration. (A) Shows a patient with a negative test; after flecainide QT is slightly prolonged in both the right and left precordial leads. (B) Shows a patient with a positive test; note the marked prolongation of QT in the right precordial leads, which is greater than that observed in the left precordial leads.
formers (13). In order to increase the probability of detecting the presence of any sequence changes, the SSCP analysis was carried out at two different temperatures (5°C and 20°C) and three different buffer pH values (7.5, 8.6, and 9.0) for each exon. A panel of 60 unrelated healthy individuals (120 chromosomes), coming from the same geographic area (Southern Italy) was used as a control. Our local ethics committee approved the study, and written informed consent was obtained from all of the participants.

Statistical analysis. The continuous variables are presented as mean values ± SD. Reproducibility of data was evaluated by means of the intraclass correlation coefficient (ICC) (12). Thus, ICC = SD² between / (SD² between + SD² within). In particular, reproducibility was considered good if the ICC was between 0.61 and 0.80 and almost perfect if it was between 0.81 and 1. QRS durations before and after flecainide, and the mean post-flecainide changes in duration, were respectively compared by means of Student t test for dependent and independent samples. The QTc values obtained before and after flecainide and the mean changes in QTc intervals were compared by means of analysis of covariance using QRS durations as covariates. Sensitivity was defined as the number of patients with QTc prolongation after flecainide divided by the number of patients with QRS--ST-T modification after flecainide. Specificity was defined as the number of patients without QTc prolongation after flecainide divided by the number of patients without QRS-ST-T modification after flecainide. For each lead, all QTc values were used to construct receiver operator characteristics (ROC) curve by plotting its sensitivity versus its 1-specificity. The diagnostic accuracy of the QTc interval recorded in each precordial lead after flecainide administration was evaluated using the areas under the ROC curve. A p value of <0.05 was considered statistically significant.

RESULTS

The flecainide test was negative in 14 subjects (7 males; mean age, 29 ± 12 years) and positive in 18 (12 males; mean age, 43 ± 16 years).

The QRS duration and QTc intervals were significantly prolonged after flecainide administration in both the positive and negative subjects (Table 1).

The mean prolongations of longest QRS in standard leads and QTc in V₁ and V₂ were significantly greater in the positive than the negative group, whereas no between-group

### Table 1. Comparison of Electrocardiographic Parameters Before and After Flecainide Administration in Subjects With Negative and Positive Test

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<tr>
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<th>Negative Test</th>
<th>Positive Test</th>
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<td>Before Flecainide</td>
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<td>Before Flecainide</td>
<td>After Flecainide</td>
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<tr>
<td>QRS max (ms)</td>
<td>95.5 ± 12.2</td>
<td>114.5 ± 16.8*</td>
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<tr>
<td>QTc (ms)</td>
<td>392.2 ± 32.6</td>
<td>414.2 ± 30.2*</td>
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<tr>
<td>V₁</td>
<td>381.7 ± 28.5</td>
<td>404.8 ± 39.8*</td>
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<td>V₂</td>
<td>402.9 ± 37.0</td>
<td>442.6 ± 19.2*</td>
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<td>V₃</td>
<td>404.6 ± 27.8</td>
<td>443.2 ± 22.7*</td>
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<tr>
<td>V₄</td>
<td>407.7 ± 25.9</td>
<td>442.7 ± 21.0*</td>
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<td>V₅</td>
<td>408.7 ± 28.8</td>
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<td>106.8 ± 10.2</td>
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<td>400.8 ± 36.8</td>
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<td>406.2 ± 27.9</td>
<td>513.3 ± 45.1*</td>
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<td>409.1 ± 27.2</td>
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<td>416.6 ± 26.1</td>
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<td>416.2 ± 29.3</td>
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Mean±SD. *p < 0.05 vs. before flecainide values.
differences were found when QTc prolongation in V5 and V6 was considered (Fig. 2). Furthermore, in the positive group, the QTc changes from baseline in the right precordial leads were significantly greater than those in the left precordial leads (Fig. 2). No significant differences between right and left precordial lead changes were found in the negative group (Fig. 2).

The areas under the ROC curves obtained from the post-flecainide QTc in each lead are shown in Figure 3. The value of the QTc interval in V2 has the greatest accuracy in discriminating negative from positive electrocardiograms (ECG) (see text for details). (B) Distribution of QTc intervals in V2 after flecainide administration. A QTc interval in V2 of >464 ms in females and >442 ms in males identified a positive ECG with 100% sensitivity and specificity. Closed circles = females with a positive test; open circles = females with a negative test; closed triangles = males with a positive test; open triangles = males with a negative test.

Figure 3. (A) Receiver operator characteristic curves obtained from the post-flecainide QTc in each lead. The value of the QTc interval in V2 has the greatest accuracy in discriminating negative from positive electrocardiograms (ECG) (see text for details). (B) Distribution of QTc intervals in V2 after flecainide administration. A QTc interval in V2 of >464 ms in females and >442 ms in males identified a positive ECG with 100% sensitivity and specificity. Closed circles = females with a positive test; open circles = females with a negative test; closed triangles = males with a positive test; open triangles = males with a negative test.

During the systematic survey of all of the SCN5A gene exons, one missense mutation changing the coding from arginine to histidine (R282H) in exon 7 (14) was identified in three subjects belonging to the same family: two had an abnormal flecainide-induced ECG pattern with QTc prolongation; the third did not have a positive flecainide-induced ECG pattern but only a marked QTc prolongation in V2 (464 ms). This sequence change identified in a single family was not found in 120 chromosomes of normal subjects or in the chromosomes of the remaining probands and family members.

DISCUSSION

The diagnosis of Brugada syndrome depends on the spontaneous or flecainide-induced occurrence of right bundle branch block, coved-type ST-segment elevation, and T-wave inversion in the right precordial leads (1–3). This study adds a new element to the typical ECG pattern, that is, it is always associated with a considerable prolongation of right ventricular repolarization.

The relevance of our finding comes from the fact that it
is in accordance with the electrophysiological changes that have been hypothesized as occurring in the presence of the altered ionic currents caused by the disease. In Brugada syndrome, the inherited predominance of the outward repolarizing current at the end of phase 1 (3,14,15) exaggerates the electrical heterogeneity existing within the ventricular wall in physiological states. Under normal conditions, a different balance between inward and outward currents makes the notch more prominent in the right than the left epicardium, and in the epicardium than in the endocardium (16–19). Given that the greater the baseline AP notch, the longer the induced AP prolongation, the AP in Brugada patients should be mainly prolonged in the right epicardium. The suggested mechanism underlying this phenomenon is the presence of a more marked shift of phase 1 toward more negative potentials; this reduces the availability of calcium current, leading to delays in the emergence of the second upstroke and the onset of phase 3 and, therefore, a marked prolongation of AP duration (20,21).

We suggest that the prolongation of the QT interval in concomitance with the appearance of coved-type ST-segment elevation is the electrocardiographic manifestation of these electrophysiological abnormalities. This interpretation is supported by the fact that there was a strict association between the lengthening of the QT interval and the typical ECG pattern: the QT interval was normal when the baseline ECG did not show any coved-type ST-segment elevation, but when flecainide induced the typical ECG pattern, prolonged repolarization appeared because the drug unmasks the inherited ionic defect. The prolongation of repolarization after flecainide was mainly evident in the right precordial leads but, although smaller, could also be seen in the left. This is in line with cellular electrophysiology: inhibition of the sodium current should also prolong AP duration in the left epicardium—but to a lesser extent than in the right epicardium (19). On the basis of these considerations, we suggest that QT prolongation in the right precordial leads is a specific element of the typical ECG pattern recorded in Brugada patients, a hypothesis that is strengthened by the finding that spontaneously occurring typical ECGs are also characterized by a long QTc interval in these leads (Fig. 4).

A small post-flecainide prolongation of the QTc interval was also found in negative ECGs. This may have been due to drug-induced QRS lengthening (22,23), but we cannot exclude the possibility that, at least in some subjects, genetic ionic abnormalities may play a role. A number of mutations in the SCN5A gene encoding the cardiac sodium channel alpha-subunit have been causally linked to a percentage of between 10% and 30% of Brugada patients and their relatives (24). The finding of QTc prolongation strictly associated with the typical ECG pattern regardless of the presence or absence of an SCN5A mutation suggests that the repolarization phase at surface ECG is prolonged every time the magnitude of the AP notch increases. This happens whatever the candidate gene mutations supposed to be involved in causing abnormal ion channel activation during phase 1 of the AP. In our series, three subjects were R282H mutation carriers, as reported by Priori et al. (14): two had a typical flecainide-induced ECG associated with marked QTc prolongation in the right precordial leads; in the third, flecainide induced QTc prolongation in V1 and V2 (the longest among the negative ECGs) without the typical ECG features. The association between the R282H mutation and post-flecainide QT prolongation in the absence of ST-segment elevation suggests that SCN5A mutations carrier without baseline or flecainide-induced typical ECG pattern (25) may show a prolonged QT. If this is the case, mutation carriers with a different expression and, therefore, different susceptibility to sodium channel inhibition also have different ECG pictures. In particular, those characterized by a higher expression would have a typical flecainide-induced ECG pattern and QT prolongation, whereas QT prolongation alone may be the result of a lower expression. This hypothesis is supported by what happens when increasing sodium current inhibition is produced in experimental models. A small inhibition is associated with a prolonged AP, whereas a high level of inhibition is associated with a marked shortening of the AP (20,21). On the basis of our results, it can be suggested that the former electrophysiological modification is responsible for QT prolongation alone and the latter for coved-type ST-segment elevation (3). The coexistence of these electrophysiological effects justifies the coexistence of both ECG findings.

These findings might be further explored in future studies evaluating the usefulness of flecainide-induced QTc prolongation in classifying doubtful ECGs, thus making it possible to shed new light on the pathophysiology of Brugada syndrome.

In conclusion, we have demonstrated that the typical ECG pattern of Brugada syndrome is characterized by coved-type ST-segment elevation and QT prolongation in the right precordial leads.

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