Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)01118-5

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

Maria Vittoria Pitzalis, MD, PHD,*† Matteo Anaclerio, MD, PHD,* Massimo Iacoviello, MD,* Cinzia Forleo, MD, PHD,* Pietro Guida, MS,* Rossella Troccoli, MD,* Francesco Massari, MD,‡ Filippo Mastropasqua, MD,‡ Sandro Sorrentino, PHD,* Andrea Manghisi, MS,* Paolo Rizzon, MD*†

Bari and Cassano, Italy

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 V_1 and 107.1 ± 43.8 ms vs. 26.7 ± 30.1 ms in V_2; $p < 0.01$), 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 V_5 and 53.1 ± 32.8 ms vs. 27.3 ± 22.4 ms in V_6; 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.

From the *Institute of Cardiology, University of Bari, Bari, Italy; †Centre of Innovative Technologies for Signal Detection and Processing, University of Bari, Bari, Italy; and the ‡Cardiology "Salvatore Maugeri" Foundation, IRCCS Cassano, Cassano, Italy.

Manuscript received March 25, 2003; revised manuscript received June 6, 2003, accepted July 1, 2003.

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-

Abbreviations and Acronyms

AP = action potential
ICC = intraclass correlation coefficient
PCR = polymerase chain reaction
QTc = QT interval corrected for heart rate
ROC = receiver operator characteristics
SSCP = single-strand conformation polymorphism

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 V_1 to V_2 (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 ms 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 V_1 to V_6 (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 V_1 to V_6 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-

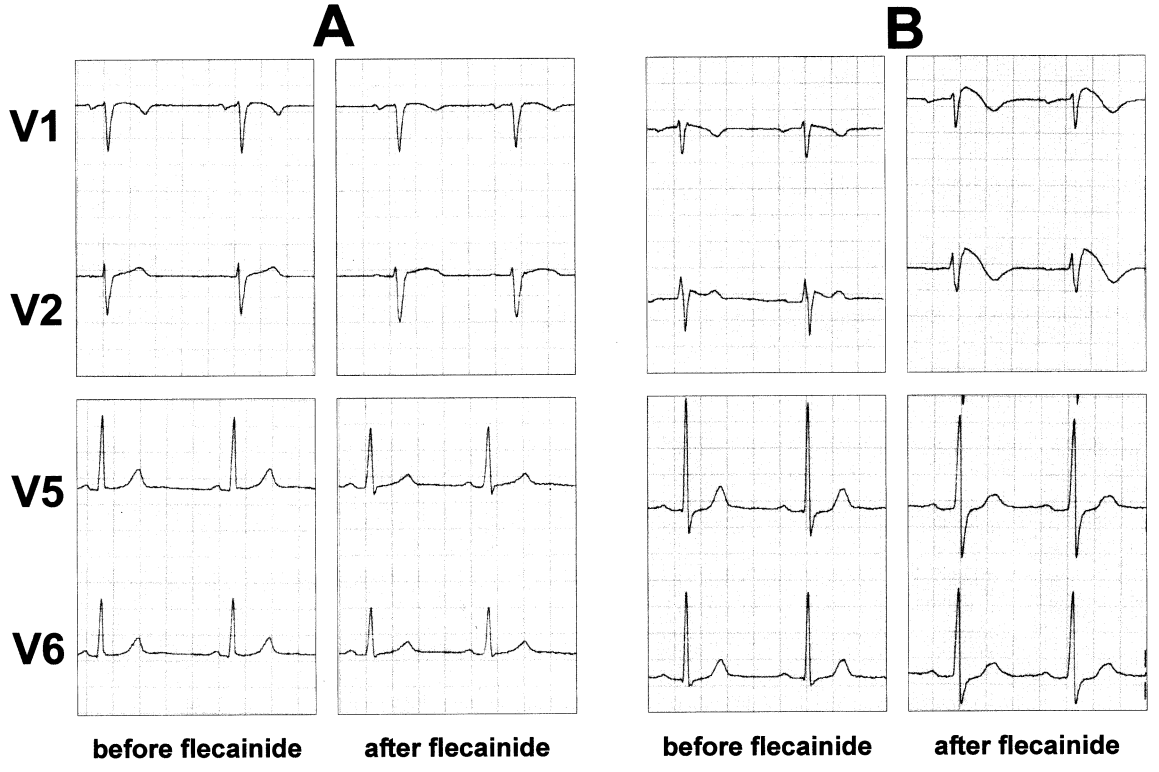

Figure 1. Right and left precordial leads at baseline and after flecainide administration. **(A)** Shows a patient with a negative test; after flecainide QT is slightly prolonged in both the right and left precordial leads. **(B)** Shows a patient with a positive test; note the marked prolongation of QT in the right precordial leads, which is greater than that observed in the left precordial leads.

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

	Negative Test			Positive Test		
	No.	Before Flecainide	After Flecainide	No.	Before Flecainide	After Flecainide
QRS max (ms)	14	95.5 ± 12.2	114.5 ± 16.8*	18	106.8 ± 10.2	132.7 ± 17.8*
QTc (ms)						
V_1	14	392.2 ± 32.6	414.2 ± 30.2*	18	400.8 ± 36.8	479.0 ± 36.6*
V_2	14	381.7 ± 28.5	408.4 ± 39.8*	18	406.2 ± 27.9	513.3 ± 45.1*
V_3	14	402.9 ± 37.0	442.6 ± 19.2*	17	409.1 ± 27.2	473.7 ± 44.7*
V_4	14	404.6 ± 27.8	443.2 ± 22.7*	18	416.6 ± 26.1	471.2 ± 46.3*
V_5	14	407.7 ± 25.9	442.7 ± 21.0*	18	417.4 ± 26.8	472.6 ± 27.8*
V_6	14	408.7 ± 28.8	435.9 ± 20.0*	18	416.2 ± 29.3	469.3 ± 26.8*

Mean±SD. *$p < 0.05$ vs. before flecainide values.

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 = $SD^2_{between}$ /($SD^2_{between}$ + SD^2_{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 V_1 and V_2 were significantly greater in the positive than the negative group, whereas no between-group

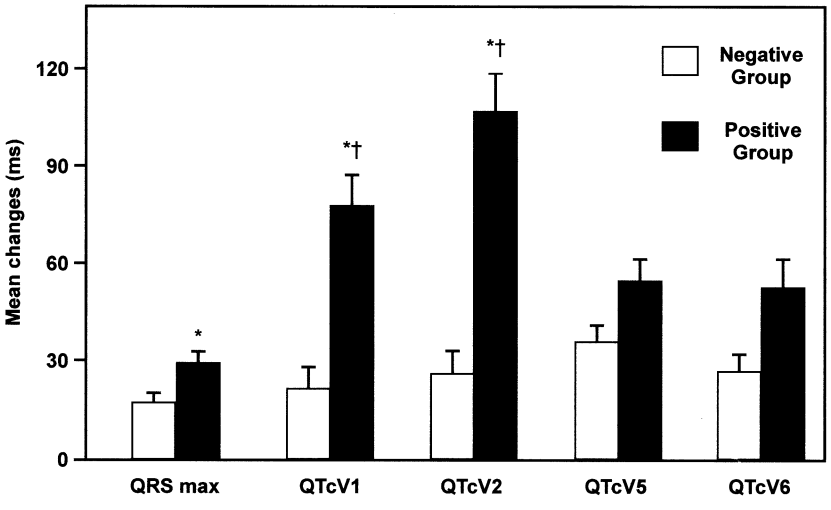

Figure 2. QRS and QTc changes from baseline recorded in the right and left precordial leads in the negative (**white columns**) and positive groups (**grey columns**). Data expressed as mean values ± SE. *$p < 0.01$ vs. negative group; †$p < 0.01$ vs. $QTcV_5$, $QTcV_6$.

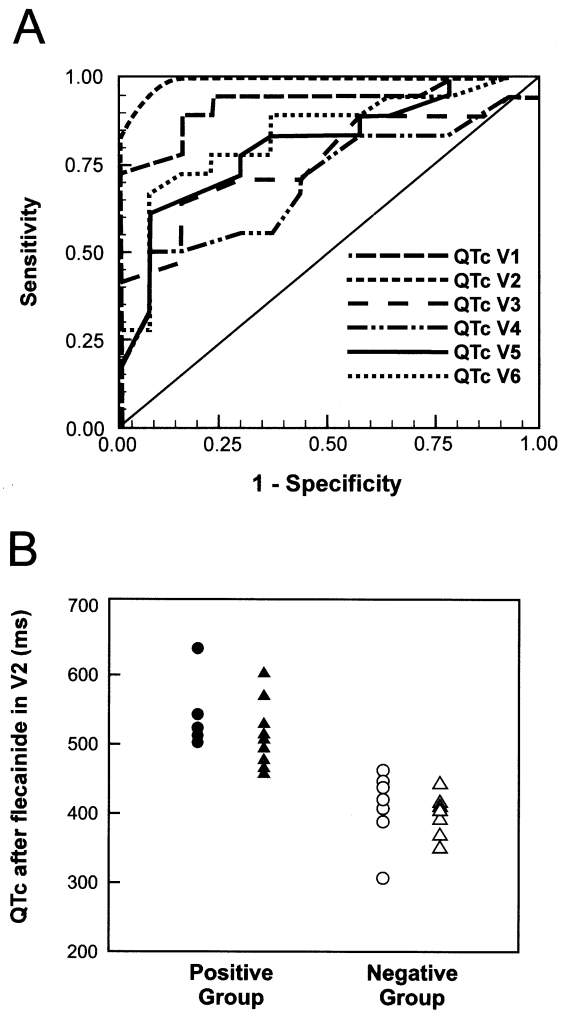

Figure 3. (A) Receiver operator characteristic curves obtained from the post-flecainide QTc in each lead. The value of the QTc interval in V_2 has the greatest accuracy in discriminating negative from positive electrocardiograms (ECG) (see text for details). **(B)** Distribution of QTc intervals in V_2 after flecainide administration. A QTc interval in V_2 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.

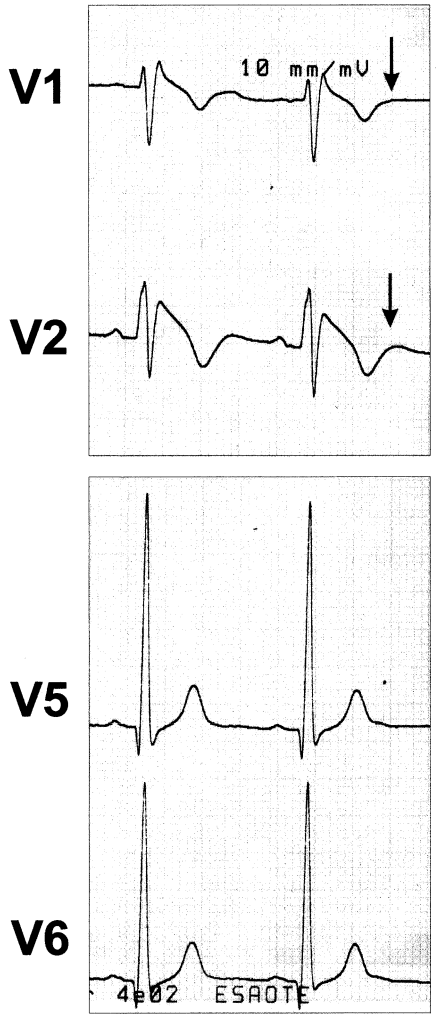

Figure 4. Right and left precordial leads recorded in a patient with a baseline typical electrocardiogram pattern. The end of T wave in V_1 and V_2 is illustrated by the **arrows**.

differences were found when QTc prolongation in V_5 and V_6 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 area under the ROC curve of the QTc in V_1 was 0.93, that in V_2 0.99, in V_3 0.76, in V_4 0.70, in V_5 0.81, in V_6 0.83. The largest area was that found in V_2, and the best cutoff (460 ms) had a sensitivity of 100% in identifying subjects with a positive test, a specificity of 93%, and an accuracy of 97%.

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 V_2 (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 V_1 and V_2 (the longest among the negative EGCs) 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 mutation carriers 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.

Acknowledgments

The authors thank Mr. Cataldo Balducci and Ms. Angela Burdi for their helpful technical assistance.

Reprint requests and correspondence: Dr. Maria Vittoria Pitzalis, Institute of Cardiology-University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy. E-mail: mariavittoria.pitzalis@cardio.uniba.it.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 1992;20:1391–6.
2. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510–5.

3. Antzelevitch C. The Brugada syndrome: diagnostic criteria and cellular mechanisms. Eur Heart J 2001;22:356–63.
4. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100:1660–6.
5. Shimizu W, Antzelevitch C, Suyama K, et al. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11:1320–9.
6. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V_1 to V_3. Circulation 2002;105:73–8.
7. Bayés de Luna A. Normal QRS complex. In: Clinical Electrocardiography: A Textbook. Mount Kisco, NY: Futura Publishing Company, Inc., 1993:78–93.
8. Surawicz B. Long QT interval, torsade de pointes and early afterdepolarizations. In: Electrophysiologic Basis of ECG and Cardiac Arrhythmias. Malvern, PA: Williams & Wilkins, 1995:191–229.
9. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. J Cardiovasc Electrophysiol 1994;5:672–85.
10. Langley P, Di Bernardo D, Murray A. Effect of lead exclusion for the manual measurement of QT dispersion. Pacing Clin Electrophysiol 2001;24:75–81.
11. Surawicz B. Abnormalities of ventricular repolarization. In: Electrophysiologic Basis of ECG and Cardiac Arrhythmias. Malvern, PA: Williams & Wilkins, 1995:566–607.
12. Fleiss JL. The Design and Analysis of Clinical Experiments. New York, NY: Wiley, 1986:5–12.
13. Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. Genomics 1996;34:9–16.
14. Priori S, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–7.
15. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392: 293–6.
16. Litovsky SH, Antzelevitch C. Transient outward current prominent in canine ventricular epicardium but not endocardium. Circ Res 1988; 62:116–26.
17. Antzelevitch C, Sicouri S, Litovsky SH, et al. Heterogeneity within the ventricular wall: electrophysiology and pharmacology of epicardial, endocardial, and M cells. Circ Res 1991;69:1427–49.
18. Litovsky SH, Antzelevitch C. Rate dependence of action potential duration and refractoriness in canine ventricular endocardium differs from that of epicardium: role of the transient outward current. J Am Coll Cardiol 1989;14:1053–66.
19. Di Diego JM, Sun ZQ, Antzelevitch C. Ito and action potential notch are smaller in left vs right canine ventricular epicardium. Am J Physiol 1996;271:H548–61.
20. Krishnan SC, Antzelevitch C. Sodium channel block produces opposite electrophysiological effects in canine ventricular epicardium and endocardium. Circ Res 1991;69:277–91.
21. Krishnan SC, Antzelevitch C. Flecainide-induced arrhythmia in canine ventricular epicardium. Phase 2 reentry? Circulation 1993;87: 562–72.
22. Hellestrand KJ, Bexton RS, Nathan AW, Spurrell RA, Camm AJ. Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man. Br Heart J 1982;48:140–8.
23. Milne JR, Hellestrand KJ, Bexton RS, Burnett PJ, Debbas NM, Camm AJ. Class 1 antiarrhythmic drugs: characteristic electrocardiographic differences when assessed by atrial and ventricular pacing. Eur Heart J 1984;5:99–107.
24. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Eur Heart J 2002;23:1648–54.
25. Priori SG, Napolitano C, Gasparini M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. Circulation 2000; 102:2509–15.