Quinidine Induced Electrocardiographic Normalization in Two Patients with Brugada Syndrome

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ALINGS, M., ET AL.: Quinidine Induced Electrocardiographic Normalization in Two Patients with Brugada Syndrome. Two patients with Brugada syndrome are presented. The ECGs showed right precordial J waves and ST-segment elevation. Patient 1 was resuscitated from nocturnal ventricular fibrillation, patient 2 was asymptomatic. In only patient 1, flecainide was infused causing monomorphic “malignant” ventricular extrasystoles (R on T), demonstrating the deleterious effect of Class IC antiarrhythmic drugs in Brugada syndrome. However, administration of the Class IA antiarrhythmic drug quinidine caused normalization of the ECG in both patients. Based on in vitro experiments, agents that reduce the magnitude of Ito-mediated phase 1 have been suggested to normalize ST-segment elevation in Brugada syndrome. This is the first clinical report of such a quinidine induced ECG normalization. (PACE 2001; 24:1420–1422)

Brugada syndrome, antiarrhythmic agents, arrhythmia, quinidine, flecainide

Introduction

The Brugada syndrome is a primary electrical disease with a high risk for sudden death. Electrocardiographically (ECG), the syndrome is characterized by a J wave and ST-segment elevation in the right precordial leads. Patients are mostly in their third or fourth decade. Arrhythmic events (ventricular tachycardia/ventricular fibrillation (VT/VF)) usually occur while sleeping. Increased nocturnal vagal activity has been suggested to play a role in the arrhythmogenesis. Heterogeneity of repolarization across the right ventricle outflow tract (RVOT) is thought to underlie the syndrome. Right precordial J wave, ST-segment elevation, and arrhythmogenesis are likely to be based on differences in endo- to epicardial distribution and expression of the transient outward current (Ito). On a molecular level, however, so far mutations have been identified in the cardiac sodium channel gene SCN5A only.

In resuscitated patients, recurrences of arrhythmic events occur in 40% and cannot be prevented by drugs. Implantable cardioverter defibrillator (ICD) implantation is the only effective therapy to prevent sudden death. The role of quinidine, however, a vagolytic drug that among other potassium currents blocks Ito, remains to be established. In vitro, quinidine has been shown to normalize Ito induced ST-segment elevation. This case report describes two patients with Brugada syndrome in whom administration of therapeutic dosages of quinidine normalized J wave and ST-segment elevation in the right precordial leads.

Case Reports

Case 1

A previously healthy 37-year-old man was successfully resuscitated from nocturnal VF. Except for sporadic palpitations, suppressible by Valsalva’s maneuver, his medical and family history were unremarkable. The ECG showed sinus rhythm, 60 beats/min, electrical axis +30 degrees, PQ 0.14 seconds, and QRS 0.10 seconds. A prominent J wave was present in leads V1–2 with up to 2-mm ST-segment elevation (Fig. 1A). At admission, K+ was low (3.0 mMol/L). Within 24 hours K+ normalized as acid-based disturbances recovered. Other serum electrolytes were normal. Maximum myocardial bound creatine kinase (CKMB max) and CK max were elevated due to muscle trauma during resuscitation (14 and 733 E/L, respectively). Structural cardiac abnormalities were excluded by transesophageal echocardiography and ventricular angiography. Coronary arteries were normal. Electrophysiological study in the nonsedated baseline state showed normal sinus node and atrio-ventricular node (AVN) parameters. HV delay was normal (46 ms). VF was induced with two extrastimuli in the RVOT. Finally, the presence of known SCN5A mutations associated with Brugada syndrome was excluded using single strand conformation polymorphism (SSCP) techniques.

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ECG abnormalities in Brugada syndrome are known to transiently disappear, whereas flecainide may unmask such normalization. The effect of Class Ic drugs in the presence of stable ECG abnormalities, however, is less well established. Therefore, 3 weeks postresuscitation a flecainide challenge was performed (10 mg/min intravenously [IV]). After administration of 60 mg of flecainide, nonsustained monomorphic ventricular ectopy occurred with up to three consecutive complexes with negative QRS morphology in leads V₁, II, III, and aVF and a positive QRS morphology in leads I, aVL, and V₅–6, consistent with a focus in the lower right ventricle (Fig. 1B). Awaiting an ICD, the effect of treatment with quinidine was evaluated (400 mg 3dd). Besides modest QT prolongation (QTc 488 ms), the ECG showed complete disappearance of the right precordial J wave and ST elevation (Fig. 1C and D). T wave morphology changed from saddle-shaped to a convex curved.

Case 2

A healthy 47-year-old man presented with near syncope, which turned out to be caused by orthostasis after arising from a squatting position. Physical examination, family history, and laboratory investigations were unremarkable. Routine ECG showed sinus rhythm, 60 beats/min, electrical axis +90 degrees, PQ interval 0.32 seconds, and QRS duration 0.10 second. A J wave was present in leads V₁ and V₂ with 3.5- and 5-mm ST-segment elevation, respectively (Fig. 2A). Chest X-ray and transthoracic echocardiography were normal. Electrophysiological study in the nonseated baseline state showed normal sinus node parameters. AVN refractory period was 500 ms. HV delay was prolonged (72–78 ms). VF was induced by two extrastimuli in the right ventricular (RV) apex.

A flecainide provocation test was not performed. Awaiting ICD implantation, quinidine treatment was started. Dosages were gradually increased over 5 days to 1,500 mg daily, while frequently measuring quinidine blood levels. At increasing quinidine concentrations the ECG showed progressive diminution of the J wave (Fig. 2B). QRS duration and morphology were unaltered, whereas QTc prolonged from 420–435 ms. Quinidine blood levels significantly correlated with right preordial J wave amplitude in V₁ and V₂ (r = 0.800, P < 0.001 and r = 0.805, P < 0.001, respectively). Figure 3 exemplifies this correlation for V₂.

Discussion

The described patients represent typical examples of symptomatic and asymptomatic Brugada syndrome. In patient 1, subtherapeutic levels of flecainide caused monomorphic “malignant” ventricular extrasystoles (R on T), demonstrating the deleterious effect of Class Ic antiarrhythmic...
drugs in these patients. However, in both patients administration of therapeutic levels of the Class Ia antiarrhythmic drug quinidine caused normalization of the Brugada ECG.

In normal hearts epicardial action potentials (APs) are, in contrast to endocardial APs, characterized by an Ito-mediated "spike-and-dome" morphology. Yan and Antzelevitch already showed in their canine model that treatment with pinacidil, a K+ channel opener, caused loss of epicardial AP dome leading to J waves in the ECG. Agents that reduce the magnitude of the Ito-mediated phase 1 epicardial AP notch are expected to restore the AP dome, leading to reduction or normalization of ST-segment elevation. In vitro, quinidine and the specific Ito blocker 4-AP have been shown to restore epicardial dome and reverse pinacidil induced ST-segment elevation.5

To our knowledge these are the first clinical observations of quinidine induced right precordial ST-segment normalization in Brugada syndrome. It remains to be established, however, if ECG normalization translates into a more favorable clinical outcome. The observation by Belhassen et al.,9 that quinidine prevented induction of previously readily inducible malignant ventricular arrhythmias in four of five patients with Brugada syndrome is promising (mean follow-up 80.5 months), but larger randomized studies are needed to test the long-term safety of this approach.

References