The Electrophysiologic Mechanism of ST-Segment Elevation in Brugada Syndrome

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OBJECTIVES
We sought to demonstrate the electrophysiologic (EP) mechanism of the ST-T change in Brugada syndrome.

BACKGROUND
Brugada syndrome is characterized by various electrocardiographic manifestations (e.g., right bundle branch block, ST-segment elevation, and terminal T-wave inversion in the right precordial leads) and sudden cardiac death caused by ventricular fibrillation. Direct evidence in support of the EP mechanism underlying this intriguing syndrome has been lacking.

METHODS
Monophasic action potentials (MAPs) were obtained from three patients with the coved-type ST-segment elevation (Brugada patients) and five control patients using the contact electrode method. Epicardial MAPs were recorded during open-chest surgery in all patients.

RESULTS
A spike-and-dome configuration was documented from epicardial sites of the right ventricular (RV) outflow tract in all Brugada patients but not in control patients. Monophasic action potential recordings from the endocardium with special focus on the RV outflow tract could not demonstrate any morphological abnormalities in three Brugada patients.

CONCLUSIONS
The presence of a deeply notched action potential in the RV epicardium, but not in endocardium, would be expected to induce a transmural current that would contribute to elevation of the ST-segment in the right precordial leads. The spike-and-dome configuration may also prolong the epicardial action potential, thus contributing to a rapid reversal of the transmural gradients and inscription of an inverted T-wave.

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Published by Elsevier Science Inc. PII S0735-1097(02)01964-2

In 1992, Brugada and Brugada described a distinct subtype of idiopathic ventricular fibrillation (VF) by indicating unique electrocardiographic (ECG) manifestations characterized by right bundle branch block (late r′ wave or J-wave), ST-segment elevation of the coved or saddle-back type, and T-wave inversion in the right precordial ECG leads V1 to V2 or V3 (1–3). Since that time, great interest has been focused on the electrophysiologic (EP) mechanism of the intriguing ST-T morphology in Brugada syndrome (4–11). ST-segment elevation in Brugada syndrome has been ascribed to delayed conduction within the right ventricular (RV) outflow tract, accentuation of the action potential notch, and/or loss of the action potential dome in this region. Direct evidence in support of these EP mechanisms has been very limited and in some cases totally lacking.

Recently, Yan and Antzelevitch (12) demonstrated that depression or loss of action potential dome in the RV epicardium creates a transmural voltage gradient, which may lead to the ST-segment elevation in Brugada syndrome. Furthermore, although a few studies have investigated the repolarization property of Brugada syndrome by recording endocardial monophasic action potentials (MAP) (13,14), these were not able to completely explain the mechanism of specific ST-segment elevation in this syndrome.

To assess the direct relationship of the morphologic change in the epicardial cells on the ST-segment elevation and the resultant T-wave inversion in Brugada syndrome, we recorded MAPs from both endocardial and epicardial sites of the RV in three patients with a Brugada-type ECG.

METHODS

Subjects

Three patients with typical ECG manifestations of Brugada syndrome. Three patients with the typical ECG manifestations of Brugada syndrome were included in the present study. Patients’ clinical characteristics are shown in Table 1. Electrocardiograms obtained during sinus rhythm demonstrated a prominent coved-type ST-segment elevation followed by T-wave inversion in V1 to V2 (Fig. 1). Ventricular fibrillation was documented in Patients 1 and 2 but not in Patient 3, who had only symptomatic paroxysmal
atrial fibrillation. Although apparent organic heart disease (ventricular septal defect) was detected in Patient 2, a gene mutation of the cardiac sodium channel (SCN5A) was identified in this patient as well. Open-chest surgery was performed for various indications (Table 1). Epicardial MAPs were recorded during surgery in all patients, and endocardial MAPs were obtained during surgery (Patient 1) or during the EP study (Patients 2 and 3), which was performed several weeks before surgery.

**Five control patients with ischemic heart disease.** Five male candidates for coronary artery bypass grafting were selected as the control (Table 1). None of them had any history of myocardial infarction, syncope, or significant ventricular arrhythmia. Monophasic action potentials were recorded only from the epicardial sites during surgery.

**EP Study Protocol for the MAP Recording**

Informed consent was obtained before the MAP recordings. During constant right atrial pacing at a cycle length of 750 ms or 1,000 ms, MAPs were recorded by the contact electrode method as previously described (13–19). The MAPs and surface ECG leads were simultaneously recorded on a strip chart recorder (Siemens-Elema, Solna, Sweden, 8 channel Mingograf) or a computer/recorder system with optical disk storage (Quinton Electrophysiologic Corp., Seattle, Washington). The MAPs were amplified and filtered at a frequency of 0.05–500 or 400 Hz and were analyzed after placement of the catheter electrode in a position that provided continuous recordings with a stable amplitude (>5 mV), smooth configuration, and isopotential diastolic baseline (phase 4). The duration of MAP was determined at 90% repolarization at each recording site. Furthermore, the repolarization time was defined as the time from the onset of QRS deflection to 90% repolarization of MAP (i.e., summation of a local activation time and duration of MAP).

**Endocardial MAP recordings.** Endocardial MAP recordings were performed during the EP study (in Patients 2 and 3) or during open-chest surgery (in Patient 1). A 7-French MAP-pacing combination catheter (EP Technologies, Sunnyvale, California) was introduced through the femoral vein or artery and advanced to RV or left ventricle (LV) endocardium under fluoroscopic guidance. Monophasic action potential recordings were made from widely separated RV and LV endocardial sites (8 to 14 sites from the RV, 5 to 8 sites from the LV). An endocardial MAP from the LV was not obtained in Patient 1.

**Epicardial MAP recordings.** Epicardial MAPs were recorded by a “spatula Franz” electrode especially designed to obtain MAP during open-chest surgery (17). Immediately after the thoracotomy, we recorded epicardial MAPs from the RV anterior wall and LV anterior to lateral wall. Each recording site was approximately 5 to 15 mm apart. Because we had targeted the anterior surface of the RV, it was bathed in 37°C saline to keep the heart surface warm and close to body temperature.

**RESULTS**

Endocardial and epicardial MAP recordings in three patients with the Brugada-type ECG. **Patient 1.** In this case, endocardial and epicardial MAPs (13 epicardial and 8 endocardial sites in the RV, 7 epicardial sites in the LV) were recorded simultaneously. As shown in Figure 2, an incomplete depolarization in phase 0 and excessive upstroke in phase 2 of the epicardial MAP created a significant spike-and-dome configuration. The morphology of the MAP, which was simultaneously obtained from opposite endocardial sites of the RV outflow tract, was completely normal. Such an abnormal morphology of the MAP was recorded from neighboring epicardial sites (over an approximate 2-cm radius) of the RV outflow tract but not from other sites. The duration of the MAP and repolarization
time in the epicardial site were apparently longer than those in the endocardial site (duration of MAP, 310 ms vs. 250 ms; repolarization time, 400 ms vs. 325 ms, respectively).

PATIENT 2. During the EP study, endocardial MAPs were obtained from 22 sites (14 from the RV, 8 from the LV), but no abnormal configurations of MAPs were observed during the endocardial mapping. Epicardial MAPs were recorded from 35 sites (25 from the RV, 10 from the LV) during surgery. Epicardial MAPs obtained from the free wall of the RV outflow tract demonstrated a spike-and-dome configuration, as observed in Patient 1. Repeated MAP recordings from the same site and neighboring areas showed a particular configuration of MAP within an area of 2 to 3 cm under the pulmonary valve.

PATIENT 3. During the EP study, endocardial MAPs were obtained from 16 sites (11 from the RV, 5 from the LV). No abnormal configurations of MAPs were observed during the endocardial mapping. Epicardial MAPs were recorded from 18 sites (12 from the RV, 6 from the LV) during the Maze procedure surgery. A spike-and-dome configuration was observed from the epicardium of the RV outflow tract but not from the endocardium.

Epicardial MAP recordings in five control patients. Epicardial MAPs were obtained from both ventricles during the coronary artery bypass surgery. We recorded from 5 to 13 epicardial sites of both ventricles in each patient (mean of 9 sites) with special focus on the RV outflow tract. As shown in Figure 2, no abnormal MAPs, such as those with a spike-and-dome configuration, were demonstrated in any of the control patients.

DISCUSSION

Major findings. We demonstrated an abnormal spike-and-dome configuration of the epicardial MAPs obtained from the RVOT in three patients with the Brugada-type ECG. Incomplete depolarization during phases 0 and 1, and a deep notch in phase 2, induced a transmural current from the endocardium to the epicardium, which created a prominent J point (ST-segment) elevation. The subsequent dome produced a rapidly attenuated transmural current flow that contributed to a steep downslope (coved-type) of the ST-segment. Furthermore, a MAP and repolarization of longer duration in the epicardium than in the endocardium, resulting from a delayed dome formation, suggested a reversal current flow during phase 3 of the action potential. The longer duration of action potential in the epicardium may have created the typical terminal T-wave inversion observed in Brugada syndrome.

The mechanism of the ST segment elevation in Brugada syndrome. Yan and Antzelevitch (12) suggested that a loss of the action potential dome at the epicardium but not at the endocardium creates a transmural voltage gradient that may
In Brugada syndrome, typical ST-segment elevation is frequently recognized in leads V1 through V3 of the standard 12-lead ECG (1–14,26–28). As previously described, such a distribution indicates that the EP abnormality is located in the area around the RV outflow tract (14,28,29). In the present study, the epicardial area with a morphologic change of the MAP was compatible with the typical Brugada-ECG manifestations. Disparity in the magnitude of $I_{Ca}$ and significant notch formation during phases 0 and 1 of the RV epicardium has been reported (30). Such an intrinsic heterogeneity may be pronounced under particular conditions such as that with suppression of the sodium channels (7,23,27).

**Study limitations.** In two patients with the Brugada-type ECG, endocardial and epicardial MAPs were not recorded simultaneously. Therefore, we could not compare the duration of MAP and the local repolarization time between the epicardium and the endocardium, except for Patient 1. Because of the open-chest surgery, the precordial ECG leads ($V_1$ to $V_3$) could not be obtained during the epicardial MAP recording. However, we confirmed that the patients showed the typical Brugada ECG immediately before the chest wall sterilization in the operation room.

Although we could not completely exclude the possibility that spike-and-dome configuration of the MAP was a recording artifact, it seems unlikely, because the MAP recording maintained a stable configuration throughout the procedures and no abnormal configuration of the MAP was recorded in any of the control patients. The MAP recording technique has usually been utilized to demonstrate the action potential duration or phase 3 abnormalities such as early after-depolarization (18,19). However, theoretically, the MAP should reveal any abnormal configuration of phases 1 and 2 of the action potential if it really exists (15,16).

The MAP cannot be used to evaluate the absolute degree of transmembrane potential (16). Our assessment of the transmural current flow indicating the ST-T segment change in Brugada syndrome is therefore not based on direct measurements of the transmembrane potential.

**Clinical implication.** If the EP substrates for VF are restricted within the epicardial area of the RV outflow tract, a radical therapy such as cryosurgery may be possible for Brugada syndrome, especially in patients with multiple VF episodes after implantable cardioverter defibrillator therapy (9,26).

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**REFERENCES**


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**Figure 2.** (A) Simultaneous recording of endocardial and epicardial monophasic action potentials (MAPs) from the right ventricular outflow tract (RVOT) and electrocardiographic lead I during open chest surgery (thoracotomy implantable cardioverter defibrillator implantation) in Patient 1. In the epicardial MAP, an incomplete depolarization of phases 0 and 1, deep notch in phase 2 and delayed dome in phase 3 are observed. In contrast, a MAP obtained from an endocardial site of the RVOT exhibits a normal morphology. Because of the activation delay in the RVOT, a “notch” in the recording from the epicardium provokes a current flow from the endocardium to the epicardium at the end of QRS, which relates to J point (ST segment) elevation. The “dome” causes a rapidly attenuated or reversal transmural current, which results in a steep downslope of the ST-segment and T-wave inversion. The repolarization time in the epicardium was longer than those in the endocardium. (B) Epicardial MAPs recorded in a control patient during coronary artery bypass grafting. Despite detailed mapping around the epicardial sites of the RVOT, a “spike-and-dome” configuration was not observed in any of the patients. Endo = endocardial MAP; Epi = epicardial MAP; LAD = left anterior descending coronary artery; TV = tricuspid valve; star = pacing spike.

be responsible for the ST-segment elevation. This sole EP mechanism properly accounts for not only the ST-segment elevation but also the premature ventricular contraction (phase 2 reentry) and reentrant substrate for VF in Brugada syndrome (4–6,12).

In the present study, we documented the spike-and-dome configuration of the epicardial MAP but could not demonstrate a markedly shortened duration of MAP. However, this result is also compatible with the ECG manifestations of Brugada syndrome. Furthermore, a similar abnormal morphology of the action potential has been reported in a canine experimental model under proper conditions (flecainide infusion) (20). Considering the fact that mutations in the genes encode the cardiac sodium channels (SCN5A) and that the class Ic drug either augmented or uncovered ST-segment elevation in Brugada syndrome (1,21–25), spike-and-dome configuration of the action potential is highly possible in the clinical situation.

**Site specificity of abnormal MAP in Brugada syndrome.** In Brugada syndrome, typical ST-segment elevation is frequently recognized in leads $V_1$ through $V_3$ of the standard 12-lead ECG (1–14,26–28). As previously described, such a distribution indicates that the EP abnormality is located in the area around the RV outflow tract (14,28,29). In the present study, the epicardial area with a morphologic change of the MAP was compatible with the typical Brugada-ECG manifestations. Disparity in the magnitude of $I_{Ca}$ and significant notch formation during phases 0 and 1 of the RV epicardium has been reported (30). Such an intrinsic heterogeneity may be pronounced under particular conditions such as that with suppression of the sodium channels (7,23,27).

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