ST Segment Elevation, Ventricular Fibrillation and Coronary Spasm Induced by Acetylcholine and/or Ergonovine Maleate in Brugada Syndrome

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Running Title: ST Segment Elevation in Brugada Syndrome

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ABSTRACT

Background: Experimental studies suggested that a prominent transient outward current (I_{to})-mediated action potential notch and a subsequent loss of action potential dome in epicardium, but not endocardium, give rise to ST segment elevation and subsequent ventricular fibrillation (VF). This study examined whether patients with Brugada syndrome are sensitive to vagal stimulation or ischemia. ***Methods:*** The frequency of augmentation ($\geq$ 0.1 mV) of ST segment elevation in leads V1-V3, of induction of VF, and of induction of coronary spasm by intra-coronary injection of acetylcholine (ACh) and/or ergonovine maleate (EM) were examined in 27 symptomatic Brugada patients and 30 control patients. ***Results:*** The ST segment elevation in leads V1-V3 was augmented by 11 (33%) of the 33 right coronary injections [ACh: 6/11 (55%), EM: 5/22 (23%)] without any induction of coronary spasm, but not by any left coronary injections in Brugada patients. VF was induced by 3 (9 %) of the 33 right coronary injections [ACh: 2/11 (18%), EM: 1/22 (5%)] but not by any left coronary injections. In contrast, neither ST segment elevation in leads V1-V3 nor VF were observed in any control patients. The coronary spasm was induced in 3 (11%) of the 27 Brugada patients, and in 13 (43%) of the 30 control patients. ***Conclusions:*** Our results support the hypothesis that arrhythmogenic substrate in the right ventricular outflow tract responsible for the Brugada syndrome was sensitive to vagal stimulation or mild ischemia, resulting in an accentuated ST elevation and a precipitation of VF.

INTRODUCTION

Brugada Syndrome is characterized by an ST segment elevation in the right precordial leads (V1-V3) and an episode of ventricular fibrillation (VF).[1-16] The ST segment elevation in Brugada syndrome is usually observed in leads V1-V3, mainly V1 and V2, which reflect potentials of the right ventricular outflow tract (RVOT).[10] Recent experimental studies have suggested that a prominent transient outward current (I_{to})-mediated action potential (AP) notch and a subsequent loss of AP dome in the epicardial cell, but not the endocardial cell in the RVOT, give rise to ST segment elevation and induce subsequent VF due to phase 2 reentry.[17,18] Maintenance and loss of the AP dome, in other words, all or none repolarization is dependent on the balance of inward and outward currents active at the end of phase 1 of the AP.[19] Therefore, slight increase in an outward current [e.g., $\uparrow I_{to}$, $\uparrow$ adenosine triphosphate sensitive potassium current (I_{KATP})], or decrease in an inward current [e.g. $\downarrow$ calcium current (I_{Ca}), $\downarrow$ fast sodium current (I_{Na})] is expected to increase the magnitude of the AP notch and lose the AP dome, thus augmenting the ST segment elevation and inducing VF in Brugada syndrome.[19-23]

Vasospastic angina is reported to be associated with the Brugada syndrome in some case reports.[24,25] As VF is occasionally observed also in patients with vasospastic angina, vasospastic angina needs to be ruled out to confirm the diagnosis as Brugada syndrome.

In this study, we sought to examine the hypothesis that $\uparrow I_{KATP}$ and/or $\downarrow I_{Ca}$ may enhance the ST segment elevation in the right precordial leads and induce VF in patients with Brugada syndrome secondary to vagomimetic action or ischemia induced by intra-coronary injection of acetylcholine (ACh) and/or ergonovine maleate (EM), especially by injection to the right coronary artery which perfuses to the RVOT. The another purpose of this study was to evaluate systematically the frequency of induced coronary spasm in patients with Brugada syndrome.

METHODS

Study Population

Twenty seven patients with symptomatic Brugada syndrome were admitted and underwent coronary angiography in the National Cardiovascular Center, Osaka, Japan between 1992 and 2001.[26] They were 26 males and 1 female ranging in age from 21 to 63 (47 ± 13) years old. All 27 patients had episodes of syncope without any prodrome including chest pain, or a history of aborted cardiac arrest with or without documentation of VF. No structural heart diseases were found by physical examination, chest roentgenogram, laboratory values, echocardiographic study with wall motion analysis and doppler screening, cardiac catheterization with left and right ventriculography in any patients. All 27 patients showed spontaneously-documented persistent or transient ST segment elevation (coved or saddle-back type) in the right precordial leads V1-V3 with or without some degree of right bundle branch block (RBBB) and a corrected QT interval < 440 msec. Among the 27 patients, 9 patients showed normal QRS duration, 10 patients incomplete RBBB, and 8 patients complete RBBB. All 27 patients had episodes of syncope, and 14 patients had a history of aborted cardiac arrest. VF was documented in 14 patients, and 4 patients had family members who died suddenly. As a control group, 30 subjects, who had chest pain or chest discomfort and were suspected to be vasospastic angina, were randomly extracted. They were all males, ranging in age from 38 to 75 (60 ± 11) years old. They included 4 patients with incomplete RBBB (100 msec = or < QRS duration < 120 msec), and 2 with complete RBBB (QRS duration = or > 120 mesec).

Administration of ACh and/or EM into the coronary artery

All protocols were reviewed and approved by our Ethical Review Committee, and a written informed consent was obtained from all patients. Before the coronary angiography, all drugs including nitroglycerin and calcium antagonists were discontinued for at least 5 half-lives of each drug. The patients were in the supine rest state and underwent coronary angiography by Judkins's technique. The left coronary angiography in the right anterior oblique projection and the right coronary angiography in the left anterior oblique projection were performed under the baseline condition without injection of nitroglycerin in a standard manner. An electrode catheter was positioned in the right ventricular apex and connected to a pacemaker for back-up pacing (40 beats/minute). We first injected ACh, which was diluted in 10 ml of 0.9 % saline and was raised to 37 °C, into the right coronary artery and then into the left coronary artery. ACh was injected over 20 seconds in incremental doses of 20 and 50 μg within 2 minutes' interval. We injected EM into the right coronary artery and then into the left coronary artery in incremental doses of 10, 20, and 40 μg in the same manner. The EM study was performed at least 10 minutes after the completion of the ACh injection. We injected ACh alone in 6 patients, EM alone in 15 patients, and both ACh and EM in the remaining 6 patients in the Brugada group. In the control group, we injected ACh alone in 6 patients and EM alone in the remaining 24 patients. A 12-leads ECG and arterial blood pressure were continuously monitored before and after injection of ACh or EM. When the patients had chest discomfort, or the ST segment was elevated or depressed in any leads, or after the injection of the maximum dose of ACh or EM to each coronary artery was completed, coronary angiography was performed to assess the presence or the absence of coronary spasm. If coronary spasm was induced but was not resolved spontaneously, 200 μg of nitroglycerin was injected into the coronary artery with spasm.

Parameters

The frequency of augmentation of ST segment elevation in leads V1-V3, of induction of VF, and of induction of coronary artery spasm were evaluated. The coronary artery spasm was assessed at total or near total occlusion focally. We defined the positive augmentation of ST segment elevation in leads V1-V3 as a ≥ 0.1 mV increase in the amplitude of ST segment 20 msec after the end of QRS in any V1, V2, or V3 leads after injection of ACh or EM.

RESULTS

Augmentation of ST segment elevation induced by ACh and/or EM

Figure 1 shows augmentation of ST segment elevation by ACh injection into the right coronary artery in 2 Brugada patients. In both cases, the baseline ECG shows coved or saddle-back type ST segment elevation in leads V1 and V2. An injection of 50 μg ACh augmented the ST segment elevation in leads V1 and V2 without any induction of coronary spasm. Figure 2 shows 6 precordial leads ECG in 2 Brugada patients in whom ACh and then EM were injected. In both cases, the ST segment elevation was augmented by the right coronary injection of 50 μg ACh without any induction of coronary spasm, but not by the right coronary injection of 40 μg EM.

In the Brugada group, the ST segment elevation in leads V1 to V3 was augmented by 6 (55 %) of 11 right coronary injections of ACh, and by 5 (23 %) of 22 right coronary injections of EM, and this was not associated with any induction of coronary spasm (Figure 3A). The augmentation of the ST segment elevation localized in leads V1 to V3 was never induced by the left coronary injection of ACh or EM. The ST segment elevation in leads V1-V3 was not observed by either ACh or EM injection in any control patients (Figure 3B). The augmentation of ST segment elevation could be evaluated by both ACh and EM in 6 Brugada patients. The ST segment elevation in leads V1-V3 was augmented by 4 (67 %) of 6 injections of ACh, but only one (17 %) of 6 injections of EM (Figure 4A).

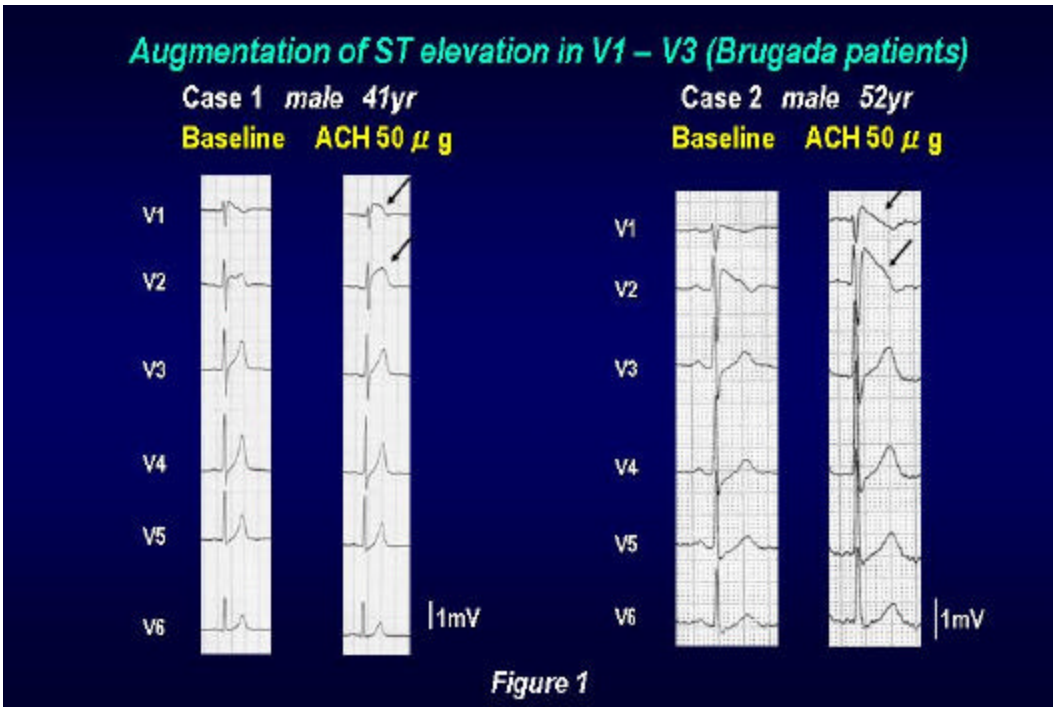

Figure 1. Six precordial leads electrocardiogram (ECG) under the baseline conditions, after injection of 50 μg acetylcholine (ACh) into the right coronary artery in two Brugada patients. The baseline ECG shows coved or saddle-back type ST segment elevation in leads V1 and V2 in both cases. Injection of ACh augmented the ST segment elevation in leads V1 and V2 (**arrows**) without any induction of coronary spasm.

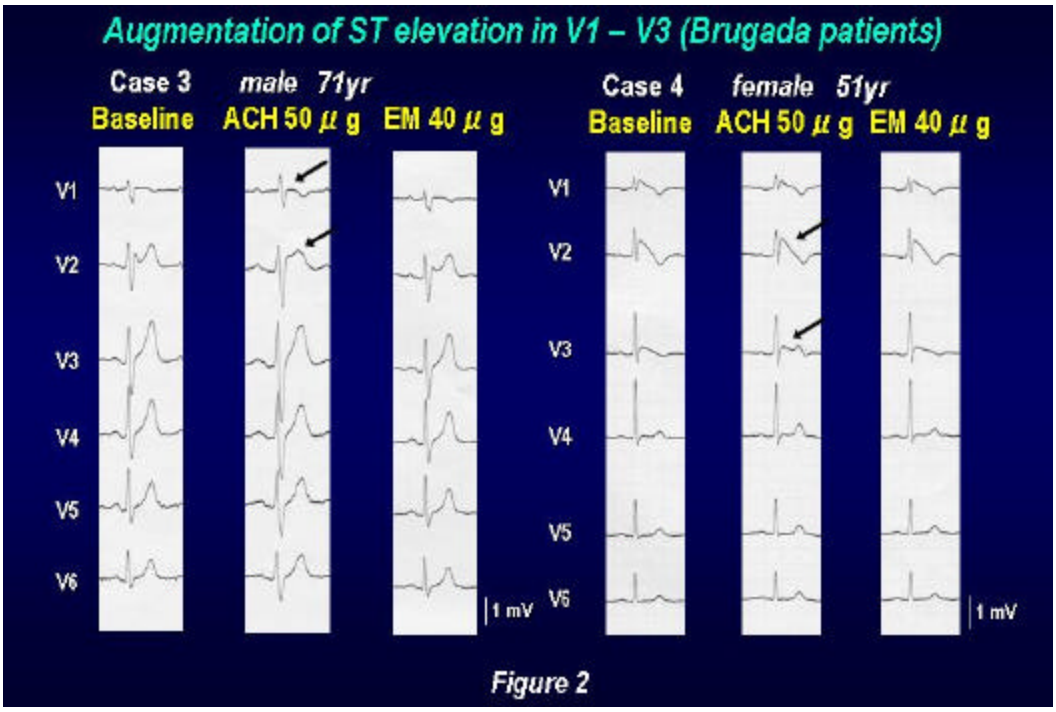

Figure 2. Six precordial leads electrocardiogram (ECG) under the baseline conditions, after injection of 50 μg acetylcholine (ACh) into the right coronary artery, and after injection of 40 μg ergonovine maleate (EM) into the right coronary artery in two Brugada patients. In both cases, injection of ACh augmented the ST segment elevation in leads V1 - V2 (V3) without any induction of coronary spasm (**arrows**), whereas injection of EM did not change the ST segment elevation.

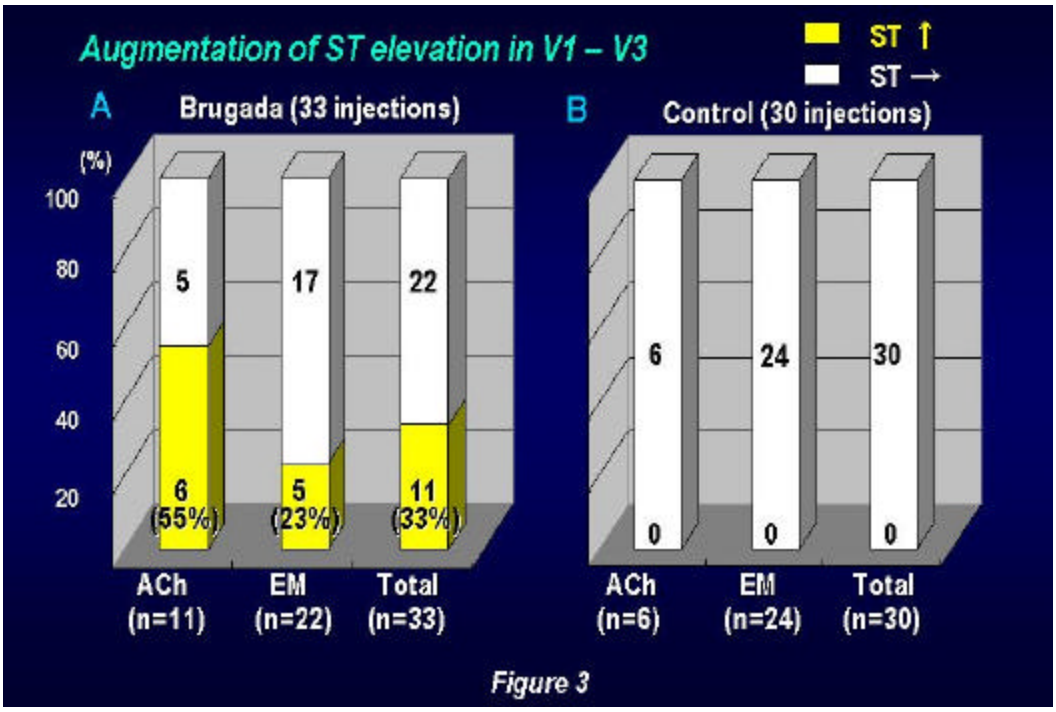

Figure 3. Frequency of augmentation of ST segment elevation in leads V1-V3 in the Brugada group (**A**) and the Control group (**B**). ACh, acetylcholine; EM, ergonovine maleate.

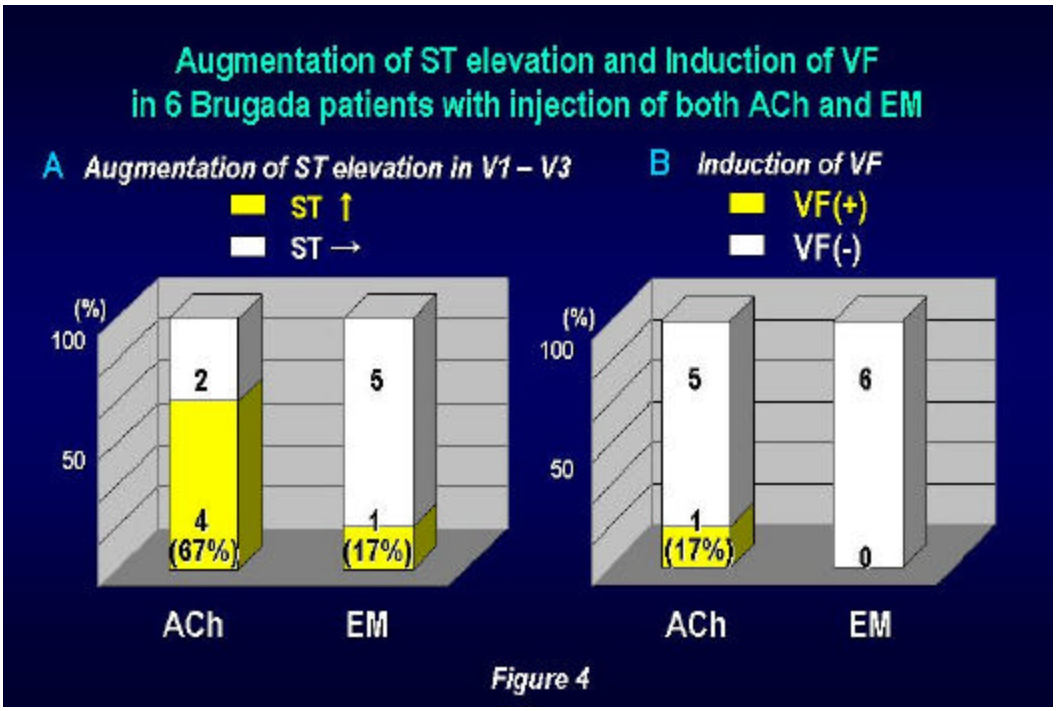

Figure 4. Frequency of augmentation of ST segment elevation in leads V1-V3 (**A**) and of induction of ventricular fibrillation (VF) (**B**) in the 6 Brugada patients in whom both acetylcholine (ACh) and ergonovine maleate (EM) were evaluated.

VF induced by ACh and/or EM

In the Brugada group, VF was induced by 2 (18 %) of the 11 right coronary injections of ACh, and by 1 (5 %) of 22 right coronary injections of EM, and this was not associated with any induction of coronary spasm (Figure 5A). VF was not induced by the left coronary injection of either ACh or EM. In contrast, VF did not occur in any control patients (Figure 5B). Among the 6 Brugada patients in whom both ACh and EM were evaluated, VF was induced by one (17 %) of 6 right coronary injections of ACh, but not by the right coronary injections of EM (Figure 4B).

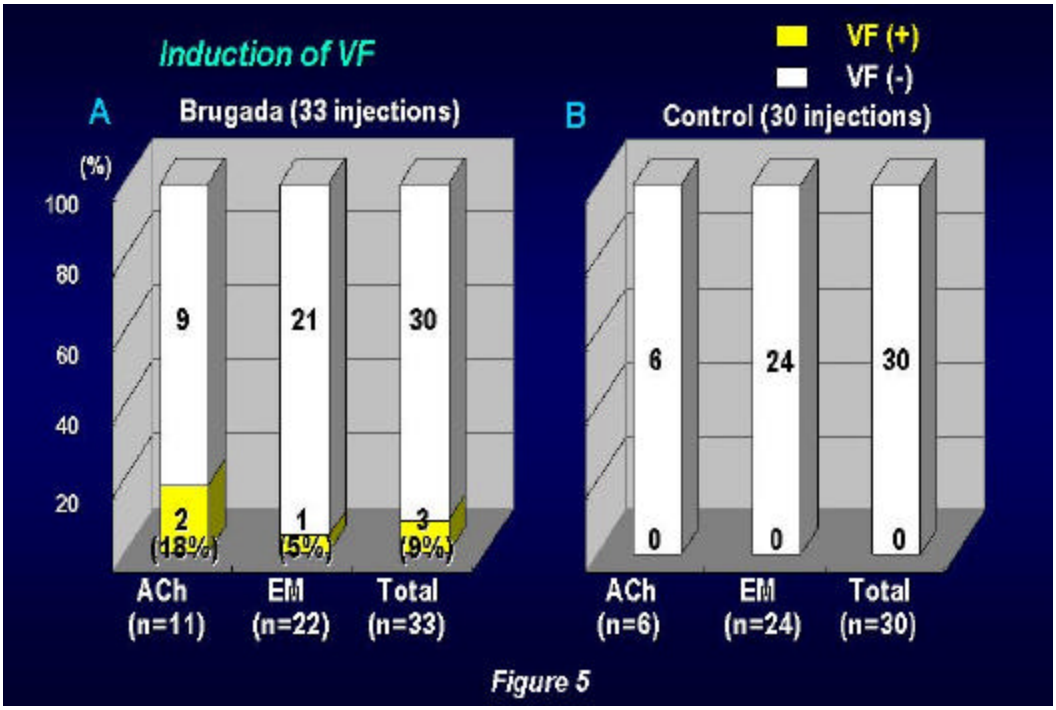

Figure 5. Frequency of induction of ventricular fibrillation (VF) in the Brugada group (**A**) and the Control group (**B**). ACh, acetylcholine; EM, ergonovine maleate.

Coronary artery spasm induced by ACh and/or EM

No significant organic stenosis of the right and left coronary arteries was observed under the baseline condition in both groups. The coronary spasm was induced in 3 (11 %) of the 27 Brugada patients (Figure 6A). The right coronary spasm (segment 1, 100 %) was induced by the right coronary injection of ACh in one patient. The left coronary spasm was induced by the left coronary injection of ACh in one patient (segment 7, 90 %), and by that of EM in the remaining one patient (segment 6, 99 %). In contrast, coronary spasm was induced by 4 (67 %) of 6 ACh injections, and by 9 (38 %) of 24 EM injections in the control patients (Figure 6B).

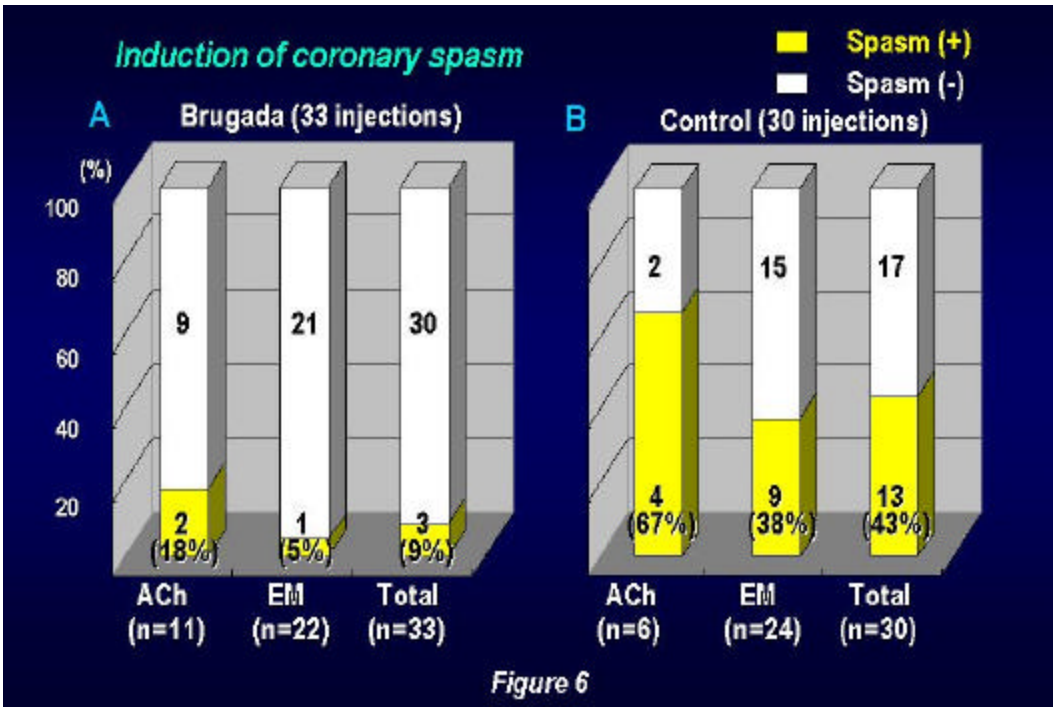

Figure 6. Frequency of induction of vasospasm in the Brugada group (**A**) and the Control group (**B**). ACh, acetylcholine; EM, ergonovine maleate.

DISCUSSION

Arrhythmogenic substrate is sensitive to vagal stimulation and/or mild ischemia

Several experimental studies have suggested that a transient outward current (I_{to})-mediated phase 1 gives rise to a notched appearance of the AP, which is more prominent in the epicardium than in the endocardium of the ventricles of many species,[19-23, 27-30] including humans.[31,32] Because the maintenance of the AP dome is determined by the balance of currents active at the end of phase 1 of the AP (principally I_{to} and I_{Ca}), any agents that cause an outward shift in current active at the end of phase 1 (e.g., $\uparrow I_{to}$, $\uparrow I_{KATP}$, $\downarrow I_{Ca}$ and $\downarrow I_{Na}$) can increase the magnitude of the AP notch, thus leading to loss of the AP dome in the epicardium, but not the endocardium.[19-23] These differential effects on tissues spanning the ventricular wall give rise to a large transmural voltage gradients soon after ventricular activation, which are thought to underlie the ST segment elevation, similar to that found in Brugada patients.[6] Experimental studies using arterially-perfused canine right ventricular wedge preparations have developed Brugada model and proved that heterogeneous repolarization across the ventricular wall of the RVOT was responsible for the ST segment elevation and

genesis of VF in Brugada syndrome.[18] Recent clinical studies from our group have also supported the hypothesis that transmural voltage gradient secondary due to accentuation of the epicardial notch and loss of the AP dome in the RVOT is responsible for the ST segment elevation in patients with Brugada syndrome.[33,34]

In this study, the ST segment elevation in leads V1-V3 was augmented by the right coronary injection of ACh or EM without any visible coronary spasm in 33 % of the symptomatic Brugada patients, but not in any control patients. It is noteworthy that the left coronary injection of ACh or EM did not accentuate the ST segment elevation in leads V1-V3 even in the Brugada patients. VF was also induced only by 3 right coronary injections of ACh or EM but not by any left coronary injections. These findings suggested that I_{to}-mediated phase 1 notch of the epicardial cells in the RVOT was sensitive to vagal stimulation ($\downarrow I_{Ca}$) produced by ACh or to mild ischemia ($\uparrow I_{KATP}$ and/or $\downarrow I_{Ca}$) induced by EM, thus resulting in the augmentation of the ST segment elevation in the right precordial leads. The right coronary injection of ACh augmented the ST segment elevation more easily than that of EM (55 % vs. 23 %). This is true in the 6 Brugada patients in whom both ACh and EM were evaluated; 4 of 6 right coronary injections of ACh, but only one of 6 right coronary injections of EM augmented the ST segment elevation, indicating more significant role of suppression of I_{Ca} by vagal stimulation with ACh in the mechanism of augmentation of ST segment elevation in the Brugada syndrome.

Incidence of induced vasospasm in Brugada syndrome

Several recent reports have demonstrated the coexistence of Brugada syndrome and vasospastic angina in single case.[24,25] Because the ST segment elevation and the subsequent VF are the clinical manifestation in both diseases, vasospastic angina needs to be excluded to diagnose the patient as Brugada syndrome. Calcium antagonists or nitrates which blocks I_{Ca} is the first choice for therapy of vasospastic angina. The administration of these agents in Brugada patients is expected to accentuate ST segment elevation and to induce VF as a result of inhibiting I_{Ca}. From this point of view, combination of vasospastic angina with Brugada syndrome should be taken into account for the management of patients with Brugada syndrome. We systematically evaluated the incidence of induced vasospasm by injections of ACh and/or EM in symptomatic patients with Brugada syndrome, and found that the induced vasospasm was not rare (11 %) in symptomatic Brugada syndrome.

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