Two Cases of Brugada Syndrome Associated With Spontaneous Clinical Episodes of Coronary Vasospasm

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Abstract

Two patients with life-threatening episodes of ventricular fibrillation (VF) showed typical ST elevation in V1-V3 leads. Both had spontaneous clinical episodes of resting angina. Intracoronary injection of acetylcholine provoked coronary vasospasm and ST elevation was the same as Brugada-type ST elevation in 1 case but not in the other. Calcium channel antagonist was prescribed to prevent coronary vasospasm but Brugada-type ST elevation and the occurrence of VF could not be prevented. The symptoms accompanied both cases. Considering these cases, the pathogenesis of Brugada syndrome should differ from that of coronary vasospasm because it could not be prevented by calcium channel antagonist.

Key words: Brugada syndrome, coronary vasospasm, ventricular fibrillation

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Introduction

The clinical importance of Brugada syndrome has been emphasized because it may cause sudden cardiac death due to ventricular fibrillation (VF) in patients without structural heart disease (1, 2). Clinical examination including coronary angiography cannot detect any abnormality in patients with Brugada syndrome, but several reports have demonstrated provokable coronary vasospasm (3-6). In this paper we described two patients with VF and symptomatic Brugada syndrome, whose chest roentgenogram, echocardiogram, thoracic magnetic resonance image (MRI) and left ventriculography did not show any sign of structural heart disease, but each patient showed spontaneous clinical episodes of coronary vasospasm.

Case 1

A 48-year-old man developed syncope and was admitted to a hospital for examination. He had been diagnosed as having hypertension and vasospastic angina 3 years earlier, and he was free from chest pain under medications with nifedipine and isosorbide dinitrate (ISDN). At 48 years old, he experienced syncope attack for a few minutes without preceding chest pain at 11:00 pm which was resting after taking a dinner. While he visited a hospital, he suddenly lost consciousness and the ECG monitor showed VF, which was successfully interrupted by direct-current (DC) shock. The 12-lead ECG showed right bundle branch block (RBBB) and coved type marked ST elevation in leads V1 through V3. ST segment was demonstrated in precordial leads (Fig. 1A) and this sometimes became the saddle-back type (Fig. 1B). The patient was diagnosed as Brugada syndrome and was transferred to our hospital for further examination (Fig. 1C).

At the time of admission to our hospital, neither physical nor neurological abnormalities were observed. Hematological and blood chemical analyses were normal except for transiently mild liver dysfunction. Treadmill exercise stress testing showed a negative result for ischemia, but the ST elevation in precordial leads improved during the exercise and returned to the previous level after the exercise. For the purpose of clinical diagnosis, all medications were once

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stopped, and then spontaneous angina occurred during the early morning in the resting state. The 12-lead ECG showed ST elevation in II, III, aVF leads (Fig. 1D). Cardiac catheterization was performed without taking any coronary vasodilators. Coronary angiogram did not show any significant stenosis. Acetylcholine (ACh) (20 μg) injection into the left coronary artery (LCA) caused LCA spasm and the ECG showed ST elevation in leads I, aVL, V5, and V6 with chest pain as the patient experienced clinically (Fig. 1F). ACh (20 μg) injection into the right coronary artery (RCA) also caused RCA spasm and the ECG showed ST elevation in leads II, III, and aVF with clinical chest pain (Fig. 1G). Intracoronary injection of ISDN could successfully release these spasms in both arteries. An electrophysiological study (EPS) was performed under treatment with ISDN. The triple extra-stimuli at the right ventricular apex induced VF which was terminated by DC shock. Intravenous injection of flecainide (50 mg/5min) augmented ST segment elevation in precordial leads (Fig. 1H) and this change was suppressed by infusion of isoproterenol.

As the treatment for vasospastic angina, diltiazem (100 mg/day) was additionally prescribed and the angina attack could be prevented completely. Although ICD implantation was recommended as the treatment for VF, the patient refused implantation. Three months later, he developed VF and could not be resuscitated.

### Case 2

A 49-year-old man developed syncope without preceding chest pain when he was resting and drinking alcohol at 10:00 pm. When an ambulance arrived, ECG monitor showed VF that was successfully terminated by DC shock. The patient was diagnosed as having vasospastic angina and nifedipine was prescribed, although the episode was not electrocardiographically documented. At admission, neither physical nor neurological abnormalities were observed except mild disorientation. Hematological and blood chemistry analyses were normal. The 12-lead ECG was normal including the ST segment in precordial leads (Fig. 2A). However, on the second hospital day, saddle-back type ST segment elevation appeared in precordial leads (Fig. 2B). Treadmill exercise stress testing showed a negative result for ischemia, but the ST elevation in precordial leads improved during the

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**Figure 1.** The 12-lead ECGs in case 1. Panels A-D show 12-lead ECGs in case 1 on the 1st, 3rd, and 7th days and during chest pain attack, respectively. Typical coved type ST elevation was observed on the 1st day (Fig.1A) but not during angina attack (Fig.1D). Panels E-H show ECG traces during catheterization. Although intracoronary acetylcholine (ACh) injection into the left coronary artery (LCA) or the right coronary artery (RCA) induced ST changes, they were different from Brugada-like ST change in this case. Intravenous injection of flecainide revealed augmented ST elevation in leads V1-V3 (Fig.1H). See text for discussion.
Figure 2. The 12-lead ECGs in case 2. Panels A and B show 12-lead ECGs on the 1st and 2nd days in case 2. Saddle-back type ST elevation was observed in V2 lead on the 2nd day (Fig.2B). Panels C-F show ECG traces during catheterization. Although intracoronary acetylcholine (ACh) injection into the left coronary artery (LCA) did not cause significant changes (Fig.2D), ACh into the right coronary artery (RCA) induced ST elevations in precordial leads and a small J wave in leads II, III, and aVF (Fig.2E) and these changes were similar to those caused by intravenous pilsicainide injection (Fig.2F). See text for discussion.

Discussion

The two cases presented in this report can be diagnosed as typical Brugada syndrome because the classical criteria for symptomatic Brugada syndrome were satisfied (7), i.e., 1) spontaneous occurrence of VF, 2) typical ST segment elevations in precordial leads, and 3) absence of structural heart disease. These cases also showed spontaneous episodes of resting angina. Although there are several reports investigating coronary vasospasm with Brugada type ECG cases (3-5), complication of clinical resting angina with symptomatic Brugada syndrome is rare. These cases comprise 2 of 8 cases of symptomatic Brugada syndrome, and the incidence of vasospasm provoked by intracoronary ACh infusion was 14/35 in Brugada type ECG cases in our institute (8).

Although both cases showed clinical episodes of VF, probably due to Brugada syndrome, and vasospastic angina, there were a few interesting differences. First, although case 2 showed coved type ST elevation in precordial leads during provoked RCA vasospasm, case 1 did not. This difference might be explained by the ischemia of the conus branch or right ventricular branches because the vasospasm in case 2 occurred at a very proximal lesion of RCA (9). Second, regardless of the provoked ischemia in RCA area, case 2 did

exercise and returned to the previous level after the exercise. Cardiac catheterization was performed for diagnosis and examination of arrhythmogenicity. Coronary angiogram did not show significant stenosis. ACh (20 μg) injection into RCA provoked to 100% obstruction at the proximal portion and the ECG showed coved type ST segment elevation in precordial leads and small J wave in leads I, II, III, and aVF with clinical chest pain (Fig. 2E). ACh (100μg) into LCA provoked 50% stenosis (not significant) (Fig. 2D). EPS was performed under treatment with ISDN. Triple extra-stimuli at the right ventricular out-flow tract induced VF that was terminated by DC shock. Intravenous pilsicainide infusion (1 mg/kg/10min) augmented ST segment elevation in precordial leads (Fig. 2F) without causing chest pain, and there was no coronary vasospasm at that time. ST elevation caused by pilsicainide was suppressed by intravenous ISP infusion. The patient was prescribed amlopidine (2.5 mg/day) additionally and an ICD was implanted.

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not show ST elevation in II, III, and aVF leads but showed small J waves in these leads. This might be explained by the earlier release from the ischemia by using intracoronary ISDN infusion in case 2, but the appearance of the J waves in inferior leads may indicate the arrhythmogenicity of the inferior area in case 2 (10-12).

The pathogeneses of the two diseases, i.e., coronary vasospasm and Brugada syndrome, might contribute to each other because the incidence of vasospasm induction in Brugada-type ECG cases is relatively higher than that in the normal population (8). However, the hypothesis that these two diseases come from the same mechanism is doubtful. Recently, it has been demonstrated that the mechanism of Brugada syndrome involves a sodium channel abnormality in at least a subset of this population (13, 14). In these cases, the action potential duration will be shortened by early closing of the sodium channel, resulting in transmural dispersion of the ventricular repolarization phase. This mechanism will increase extracellular sodium, and should result in a decrease of intercellular calcium concentration due to the action of the Na-Ca exchanger, which is the opposite of the mechanism of vasoconstriction. In the present two cases, the episodes of angina and VF did not occur at the same time, and Calcium channel antagonists could not prevent VF, although these agents successfully prevented the angina episodes. These two abnormalities are likely to have different mechanisms even though interactions between the two may occur.

One possible explanation of the accommodation of two diseases might be the influence from the activities of the autonomic nervous system. It has been reported that the ST elevation and the ventricular arrhythmogenicity become higher under the higher parasympathetic tone in Brugada syndrome (15). In contrast, coronary vasospasm has been reported to be provoked by sympathetic nervous stimulation (16), but the importance of the increase in parasympathetic activity, especially the pre-surge of the vagal tone, has also been emphasized to cause clinical vasospastic angina (17). Therefore, an increased activity of the parasympathetic nervous system might accompany these diseases in such cases. In the cases in this report, the VF episodes were both observed during resting state, so that the influence of parasympathetic activity was possible in these cases. This point might be examined by analyzing the activities of autonomic nervous system in cases Brugada syndrome.

References