# Reproducibility and diagnostic usefulness of repeated sodium channel blocker test at higher precordial electrocardiogram recording in a patient with Brugada syndrome

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## Introduction

Brugada syndrome was reported for the first time in 1992[1] and is associated with a characteristic ST-segment elevation in the right precordial leads ($V_1$–$V_3$) in the absence of demonstrable structural heart disease as well as sudden cardiac death owing to ventricular fibrillation (Vf). Brugada syndrome is diagnosed when a coved-type ST-segment elevation is observed in ≥1 right precordial lead in the presence or absence of a sodium channel blocking agent. The diagnostic criteria have been changing and the characteristics of the disease have been assessed continuously.[2,3]

It is well known that spontaneous circadian and daily variation of ST-segment morphology is observed in patients with Brugada syndrome, and the sodium channel blocker test can unmask the concealed electrocardiogram (ECG) manifestations of Brugada syndrome, which plays an important role in making the diagnosis.[2,3] However, the reproducibility of the sodium channel blocker test at the usual fourth intercostal space has not been evaluated systematically, much less at higher intercostal spaces, and there have been few reports describing the role of the repeated sodium channel blocker test for the diagnosis. In this report, we present an interesting case of a patient who exhibited different responses to the repeated sodium channel blocker test, which played an important role in the diagnosis.

## Case report

A 34-year-old Japanese man had agonal respiration when he was sleeping at nighttime, followed by cardiopulmonary arrest. Cardiopulmonary resuscitation was performed immediately by his wife. An emergency medical service team arrived at the place within 10 minutes and documented Vf, which was terminated by DC shock. The patient was subsequently transferred to our hospital for diagnostic workup. He had experienced a similar episode with agonal respiration when he was sleeping at nighttime 2 months before admission but recovered spontaneously. He had no significant medical history and had received no medication. He had no family history of Brugada syndrome or sudden cardiac death. Being 172.6 cm tall with a weight of 59.6 kg, he had a body mass index of 20.0 kg/m$^2$. An initial physical examination revealed normal findings, except for consciousness disturbance due to hypoxic-ischemic encephalopathy. The laboratory test revealed hypokalemia (plasma potassium concentration of 2.5 mmol/L), slightly increased biliary enzyme, and leukocytosis, but the other parameters were within normal limits. Chest computed tomography revealed aspiration pneumonia. He was intubated and treated with antibiotics at the emergency care unit. His body temperature was carefully monitored and maintained at less than 37°C to prevent encephalopathy worsening. His potassium level was immediately corrected by an intravenous administration of potassium. Impaired high-degree brain functions caused by hypoxic-ischemic encephalopathy and aspiration pneumonia improved in a few days.

A standard 12-lead ECG obtained 1 hour after Vf showed a slight QRS prolongation with a QRS duration of 125 ms, normal PR interval of 160 ms, and up-sloping ST depression in precordial leads from $V_2$ to $V_6$, but no other morphologic changes were found (Figure 1). Another 12-lead ECG obtained 10 hours after Vf showed early repolarization in the inferior and lateral leads with a narrower QRS duration of 110 ms (Figure 1). Further examination including chest roentgenogram, ventricular late potential analyzed using a signal-averaged ECG system, coronary angiogram, left ventriculography, and echocardiogram revealed no evidence of structural heart disease or any other abnormalities. No significant ST-segment change was observed during the treadmill exercise testing. Programmed electrical stimulation from the right ventricular apex and outflow tract could not induce Vf during an electrophysiological study. The drug challenge

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## KEY TEACHING POINTS

- Sodium channel blocker challenge test is useful for the diagnosis of Brugada syndrome. However, it demonstrates daily variation, and factors affecting the result of the test remain unknown.
- Repeated sodium channel blocker challenge tests should be considered in presumptive symptomatic Brugada patients who have not been diagnosed according to negative previous drug challenge test.
- Electrocardiogram recording of drug challenge test should be performed both at the usual and at the higher intercostal space.

test was performed with intravenous 50 mg pilsicainide, a class Ic sodium channel blocker, on the fourth admission day when no medication was prescribed except for an administration of intravenous cefazolin. ECG recordings in the supine position were performed by experienced cardiologists. Early repolarization pattern was present in the inferior leads before drug administration and saddleback-type ST-segment elevation with a J-point amplitude of 0.3 mV was provoked in lead $V_2$ at the third intercostal space after drug administration (Figure 2). At that time, the diagnostic criteria for Brugada syndrome could not be met by the result of the drug challenge test.[2] The epinephrine provocation test for congenital long QT syndrome did not induce significant QT prolongation. A 12-lead 24-hour Holter recording revealed that there was no significant spontaneous morphologic ECG change, and meals did not have any effect on the ECG morphology at the usual fourth intercostal space. The same drug challenge test using pilsicainide was performed again on the 24th admission day by the same cardiologists. Saddleback-type ST-segment elevation was observed in lead $V_2$ at the third intercostal space, with a J-point amplitude of 0.35 mV just before the test, and coved-type ST-segment elevation was induced in leads $V_1$ and $V_2$ with a J-point amplitude of 0.22 mV and 0.52 mV, respectively, after drug administration (Figure 3). Then, the diagnosis of symptomatic Brugada syndrome was established and a dual-chamber implantable cardioverter-defibrillator (ICD) was implanted.

Spontaneous coved-type ST-segment elevation was observed in leads $V_1$ and $V_2$ at the usual fourth and third intercostal spaces 1 year after Vf (Supplemental Figure 1). He has experienced 4 ICD shocks owing to Vf recurrences during the 4-year follow-up period. Every Vf occurred during the night after he had enjoyed pinball for a long time or had an intense quarrel with his wife. Quinidine bisulfate at a dose of 200 mg/day successfully suppressed Vf recurrence, but the smaller dosage of quinidine (100 mg/day) could not.

Genetic analysis using direct sequencing was performed to screen all coding exons of the *SCN5A*, *KCNQ1*, and *KCNH2* genes. It identified no abnormality in any of the *SCN5A* and *KCNH2* exons, but revealed a nucleotide change in exon 10 of *KCNQ1*, c.1343C>G, resulting in the substitution of arginine for proline at residue 448 (p.Pro448Arg), which has been reported in patients with long QT syndrome 1 and acquired long QT syndrome[4–6] and not in patients with Brugada syndrome.

## Discussion

The major finding in this case is that the diagnosis of Brugada syndrome could not be established according to the first sodium channel blocker challenge test, but the repeated drug test induced coved-type ST-segment elevation in leads $V_1$ and $V_2$ only at the higher precordial ECG recording, not at the usual intercostal space, and made it possible for us to make the early diagnosis.

We might have been able to make the diagnosis eventually, even if the second drug test had not been performed, by detecting the spontaneous appearance of coved-type ST-segment elevation at the usual intercostal space 1 year after the first cardiac event. However, the repeated drug test actually made it possible for us to make the early diagnosis and was very useful in choosing the drug for Vf recurrence. Saddleback-type ST-segment elevation was provoked after the intravenous administration of a sodium channel blocker in lead $V_2$ at the third intercostal space on the first drug test and spontaneous saddleback-type ST-segment elevation was observed in the same lead and at the same intercostal space on the second drug test. Brugada syndrome is not diagnosed in a patient with only a saddleback-type ST-segment elevation according to the HRS/EHRA/APHRS Expert Consensus Statement[3] and J-Wave Syndromes Expert Consensus Conference Report.[2] There have been no studies examining appearance timing and incidence of a spontaneous coved-type ST-segment elevation in symptomatic Brugada patients displaying a coved-type ST-segment elevation morphology only after an administration of a sodium channel blocker. Our case might indicate that the repeated drug test is needed for the diagnosis in some patients with Brugada syndrome, and the spontaneous or drug-induced saddleback-type ST-segment elevation at the higher or usual intercostal space in patients with Vf is indicative of the need for a repeated drug challenge test.

It has been reported that the reproducibility of the drug challenge test might be less than 100%,[7] and there are no previous studies examining the reproducibility of the test at the higher intercostal space. The result of the first sodium channel blocker test was negative, and a diagnostic ECG pattern was induced on the second drug test. The morphology of ST-segment elevation in patients with Brugada syndrome fluctuated spontaneously, and various factors, including changes in heart rate, body temperature, autonomic imbalance, sodium channel blockers, exercise, and food intake, have been reported to influence ST-segment elevation and morphology.[8–10] However, there have been no studies that examined the factors that can influence the sodium channel blocker test. There might be some factors that can affect the results of the drug test, just as the morphology of the ST segment is influenced by various factors. Isoproterenol,

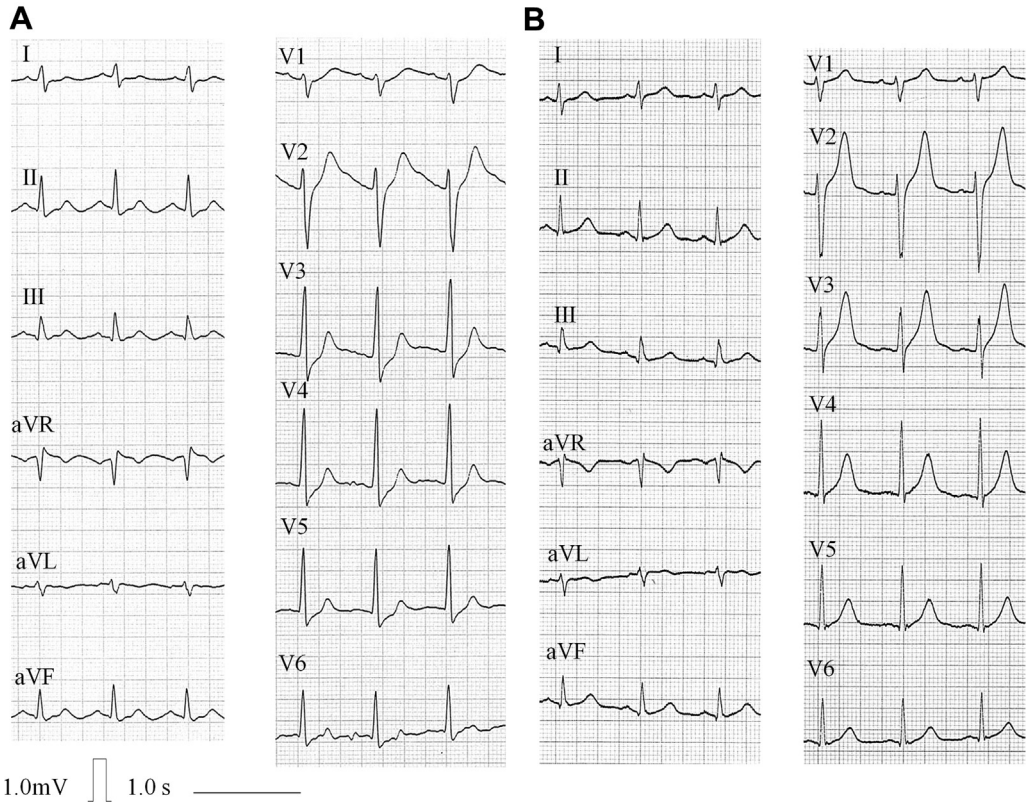


**Figure 1** **A:** A 12-lead electrocardiogram (ECG) recorded 1 hour after ventricular fibrillation showing a slight QRS prolongation with a QRS duration of 125 ms and up-sloping ST depression in precordial leads. **B:** A 12-lead ECG recorded 10 hours after ventricular fibrillation showing early repolarization in the inferior and lateral leads with a narrower QRS duration of 110 ms.

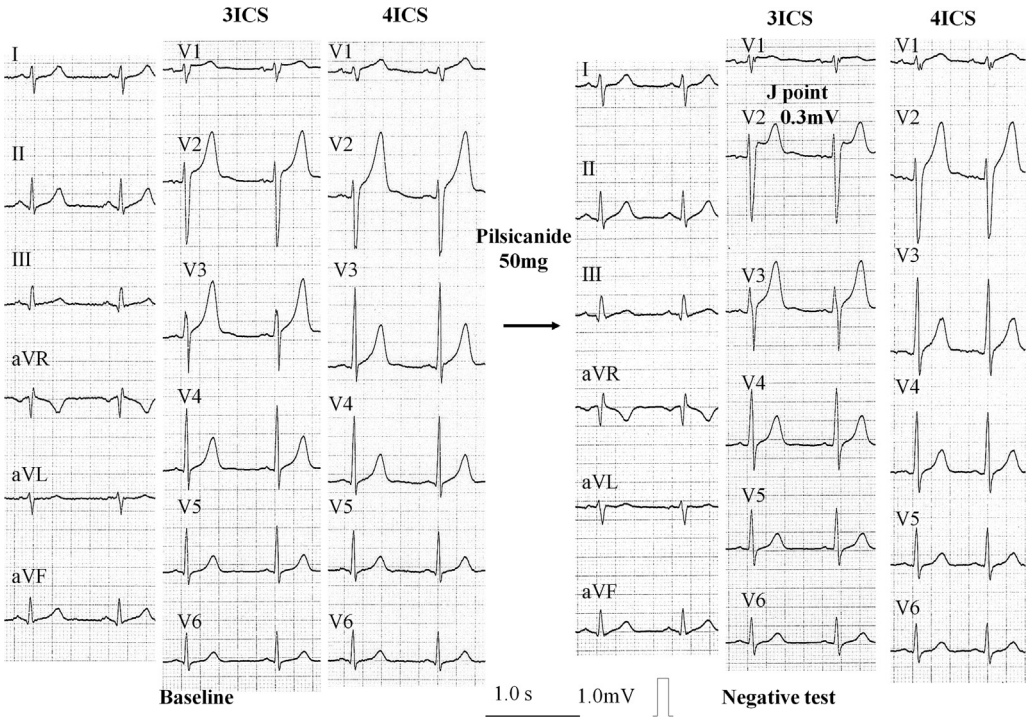


**Figure 2** Drug challenge test performed with intravenous 50 mg pilsicainide on the fourth admission day. Early repolarization pattern was present in the inferior leads before drug administration and saddleback-type ST-segment elevation with a J-point amplitude of 0.3 mV was provoked in lead $V_2$ at the third intercostal space after drug administration. 3ICS = electrocardiogram was recorded at third intercostal space in leads $V_1$, $V_2$, and $V_3$; 4ICS = electrocardiogram at fourth intercostal space.

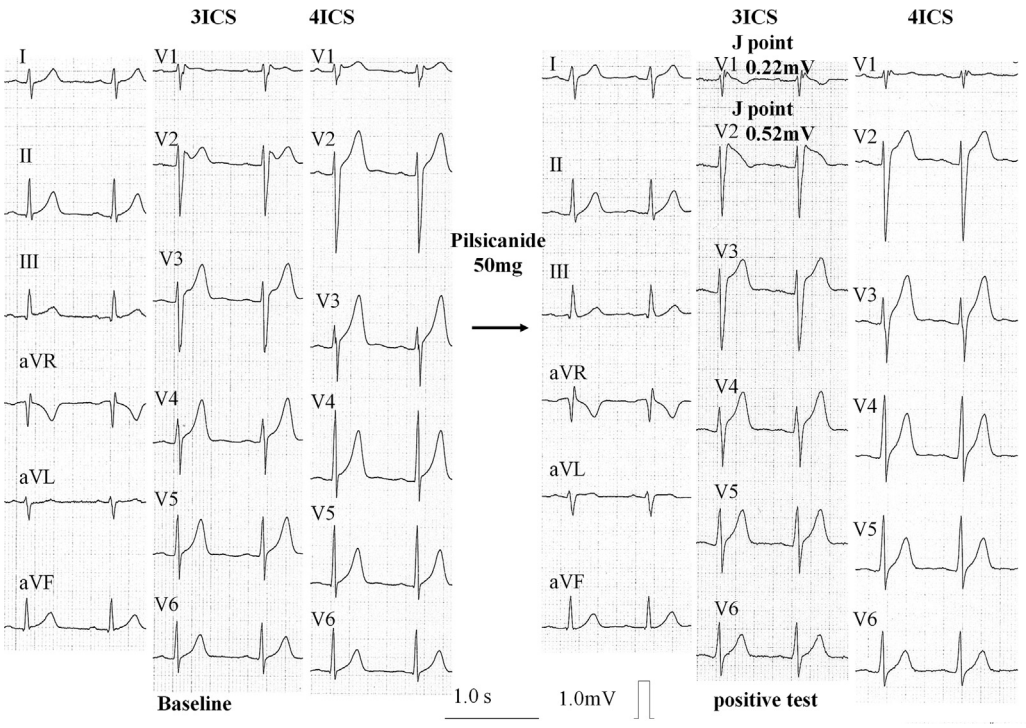


**Figure 3** Repeat drug challenge test with intravenous 50 mg pilsicainide was performed on the 24th admission day. Saddleback-type ST-segment elevation was observed in lead $V_2$ at the third intercostal space, with a J-point amplitude of 0.35 mV before drug administration, and coved-type ST-segment elevation was induced in leads $V_1$ and $V_2$ with a J-point amplitude of 0.22 and 0.52 mV, respectively, at the third intercostal space after drug administration. 3ICS = electrocardiogram was recorded at third intercostal space in leads $V_1$, $V_2$, and $V_3$; 4ICS = electrocardiogram at fourth intercostal space.

which stimulates β-adrenoceptor, has been reported to normalize the ST-segment elevation and suppress the Vf occurrence in patients with Brugada syndrome.[11] The first drug test was performed 4 days after resuscitation from the aborted sudden cardiac death, when the patient was just recovering from the aspiration pneumonia and systemic inflammation remained, with leukocytosis of white blood cell count of 15,960/μL, and his 12-lead ECG at the usual and higher intercostal space showed normal morphology and heart rate, except for early repolarization. Infection-modulated autonomic nervous activity, including increased sympathetic nervous tone, might have some effect, not only on the morphology of the 12-lead ECG at rest but also on the result of the sodium channel blocker test. Further investigations examining the factors that can modulate ST-segment elevation and the result of the sodium channel blocker test are needed to establish the more sensitive diagnostic criteria for Brugada syndrome.

A heterozygous variant (NM_000218.2:c.1343C>G, p.Pro448Arg) was detected in the *KCNQ1* gene of our patient. This variant has not been reported in Brugada patients and is highly frequent in Asian populations, including the Japanese (14%–28% allele frequency).[5,6,12] Therefore, its role in modulating the patient phenotype remains undetermined.

Our case provides information regarding the precordial leads only at the usual and third intercostal space. However, the higher precordial ECG recording at the second and third intercostal space has been shown to play an important role in the diagnosis and prognostic prediction in patients with Brugada syndrome.[13] The value of the ECG recording at both the second and third intercostal space on the drug test needs to be investigated.

## Conclusion

In the present case report, we showed the usefulness of the repeated sodium channel blocker challenge test at a higher precordial ECG recording in a patient with Brugada syndrome.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2019.01.010.

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