A Predictor of Positive Drug Provocation Testing in Individuals With Saddle-Back Type ST-Segment Elevation

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Background: A drug provocation test is performed to unmask a type 1 electrocardiogram (ECG) in individuals with saddle-back type ST-segment elevation in the right precordial leads (SB-ECG). The study investigated predictors of positive responders (PR) by drug testing.

Methods and Results: A total of 58 consecutive individuals with SB-ECG in lead V2 were enrolled and drug testing was performed. In leads V2 at standard and the third intercostal space (V2_{IC3}), the QRS duration was measured, the amplitudes of r' wave (r'), ST-segment 20 and 40 ms after the r' wave (r'20 and r'40, respectively), the bottom of the ST-segment (ST_b), the differences between r' and r'20 (r'-r'20), r' and r'40 (r'-r'40), r' and ST_b (r'-ST_b), and the descending rate of the ST-segment [(r'-r'20)/r'; DR20, (r'-r'20)/(r'-ST_b); DR20-ST_b] were also measured. Thirty-five PR had significantly longer QRS duration, larger r'20 and r'40, and smaller r'-r'20, DR20, and DR20-ST_b than negative responders. DR20 and DR20-ST_b in leads V2 and V2_{IC3} were most significantly different between 2 groups. The positive and negative predictive values of 'DR20-ST_b in lead V2_{IC3} <0.62' for prediction of positive tests were 92.3% and 81.8%, respectively.

Conclusions: In individuals with SB-ECG, DR20 and DR20-ST_b in leads V2 and V2_{IC3} might be useful predictors of positive testing. (Circ J 2009; 73: 1836–1840)

Key Words: Brugada syndrome; Drug provocation testing; Electrocardiogram; ST segment

Brugada syndrome is characterized by a ST-segment elevation in the right precordial leads and associated with sudden cardiac death secondary to rapid polymorphic ventricular tachycardia or ventricular fibrillation.¹ A recent consensus report proposed 3 types of ST-segment elevation (types 1 to 3) and indicated that a coved-type ST-segment elevation >0.2 mV (type 1 electrocardiogram (ECG)), in the presence or absence of Na channel blockers, is necessary for diagnosis of this syndrome.^{2,3} Individuals with saddle-back type ST-segment elevation in the right precordial leads (SB-ECG), which applies to type 2 or 3 ECG, are much more prevalent than those with type 1 ECG,⁴ at a rate of 58/10,000 inhabitants in Japan.⁵ Although previous reports show asymptomatic individuals with SB-ECG who exhibit a type 1 ECG under drug administration are low risk for fatal cardiac event for middle-term periods,^{6,7} long-term prognosis in those individuals is still unclear. For individuals with SB-ECG, therefore, a drug provocation test using Na channel blockers is necessary and generally considered helpful to diagnose a type 1 ECG.^{6,8,9} In some cases, the drug testing is accompanied with the risk of drug-induced ventricular tachyarrhythmias.^{3,10} It is difficult to undergo drug provocation testing for all individuals with SB-ECG because of the high prevalence. Although the differences between baseline ECG parameters of positive responders (PR) and negative

responders (NR) on the drug testing have been reported,^{11–13} it remains unclear which parameters on baseline ECG are clinically useful as predictors of test outcome. However, it has been reported that the ECG recorded at higher intercostal space is more sensitive and useful for diagnosis of Brugada syndrome than that recorded at the standard position.^{14–19}

In the present study, to avoid the risk of drug-induced ventricular tachyarrhythmias on drug testing, we analyzed baseline ECG parameters recorded at the standard position and the third intercostal space in individuals with SB-ECG, and evaluated predictors of PR on drug provocation testing.

Methods

In a total of 62 consecutive individuals with SB-ECG, we performed the drug provocation test using pilsicainide, a class Ic pure Na channel blocker, between September 2002 and December 2007. In these individuals, SB-ECG in leads V1 and V2 was exhibited in 4 and 58 individuals, respectively. In this study, we enrolled 58 individuals (55 males, mean age 51±11 years) with SB-ECG in lead V2. Of the 58 individuals, 48 individuals showed SB-ECG in lead V2 at the third intercostal space (V2_{IC3}). The remaining 10 individuals did not show type 1 ECG in lead V2_{IC3}. Patients who had exhibited a diagnostic ECG (type 1 ECG) at any

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Figure 1. The measurement parameters in leads V2 and V2ic3. r' , amplitude of the peak of r' wave. r'_{20} , r'_{40} , amplitudes of ST-segment 20 ms and 40 ms after the r' wave. ST_b , amplitude of the bottom of the ST-segment. $r'-r'_{20}$, $r'-r'_{40}$, $r'-ST_b$, differences in amplitudes between r' and r'_{20} , r' and r'_{40} , and r' and ST_b , respectively. DR_{20} and DR_{20-ST_b} , rate of descent of the ST-segment $[(r'-r'_{20})/r']$ and $(r'-r'_{20})/(r'-ST_b)$, respectively.

Table 1. Patient Characteristics

	Positive responders (n=35)	Negative responders (n=23)	P value
Age (years)	50.2±9.0	50.9±12.7	0.94
Gender (male)	34	21	0.56
Type 2 electrocardiogram	32	20	0.67
Type 3 electrocardiogram	3	3	0.67
Symptomatic patients	3	0	0.27
Family history of sudden cardiac death	5	2	0.69

time in the absence of Na^+ channel blockers at the standard position were excluded from this study. In all individuals, physical examination, chest X-p, and hematological testing yielded no abnormal findings, and no evidence of structural heart disease was detected on echocardiography. Three patients were symptomatic. One had a history of syncope, and 2 had survived sudden death. The remaining 55 individuals were asymptomatic. Seven individuals had a family history of sudden death (at less than 45 years of age). Fifty-two individuals showed a type 2 ECG, the other 6 individuals showed a type 3 ECG.

Drug provocation testing was performed with intravenous pilsicainide (1 mg/kg, 5 mg/min) in a quiet room equipped for cardiopulmonary resuscitation. Twelve-lead ECG at the standard position and precordial ECG at the third intercostal space were simultaneously recorded on a computer-based digital recorder system (CardioLab system) before and after the administration of pilsicainide. A positive response was defined as the occurrence of type 1 ECG at the standard position. The infusion was terminated when a positive response was elicited or major adverse events occurred, defined as ventricular arrhythmias or important conduction slowing (prolongation of QRS >30% of basal value).

In all 58 individuals, the following parameters in lead V2 (n=58) and V2ic3 (n=48) were analyzed on the baseline ECG: heart rate (HR), QRS duration (QRS_{V2}), the amplitude of the peak of r' wave (r'), the amplitudes of the ST-segment 20 ms and 40 ms after the r' wave (r'_{20} and r'_{40} , respectively), and the bottom of the ST-segment (ST_b). We calculated the differences in amplitudes between r' and

r'_{20} ($r'-r'_{20}$), r' and r'_{40} ($r'-r'_{40}$), r' and ST_b ($r'-ST_b$), and 2 types of the descending rate of the ST-segment; ① DR_{20} ; the number of $r'-r'_{20}$ divided by r' $[(r'-r'_{20})/r']$ and ② DR_{20-ST_b} ; the number of $r'-r'_{20}$ divided by $r'-ST_b$ $[(r'-r'_{20})/(r'-ST_b)]$. In addition, the S wave duration in lead II and QRS duration in lead V5 (QRS_{V5}) were measured. The method of measurement in leads V2 and V2ic3 is shown in **Figure 1**. All these parameters were measured at a paper speed of 100 mm/s with CardioLab software (GE Medical Systems) on a HP workstation xw8000 computer. All measured data were collected from 3 consecutive ECGs and averaged. Results were compared between PR and NR.

Quantitative values in all ECG parameters are expressed as the mean±standard deviation values. For comparisons between PR and NR, the non-parametric Mann-Whitney U-test was used. All tests were 2-sided, and statistical significance was defined as a value of $P<0.05$. For prediction of test results, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used.

Results

Patient characteristics in the 2 groups are shown in **Table 1**. There were 35 PR patients, while the remaining 23 individuals were NR. No significant adverse events occurred. All 3 symptomatic patients and 5 of the 7 individuals with a family history of sudden cardiac death were PR.

Baseline ECG parameters are shown in **Table 2**. In lead V2, compared with NR, PR exhibited significantly longer QRS duration (90.9 ± 9.1 vs 85.1 ± 6.1 ms; $P=0.01$, PR vs

Table 2. Measured Parameters on Baseline ECG in Leads V2 and V2ic3

	V2			V2ic3		
	Positive responders	Negative responders	P value	Positive responders	Negative responders	P value
n	35	23		28	20	
HR (beats/min)	59.4±9.3	64.8±12.4	0.16			
QRS duration (ms)	90.9±9.1	85.1±6.1	0.01	90.9±9.2	84.6±6.7	0.03
r' (mV)	0.38±0.14	0.42±0.20	0.45	0.50±0.24	0.53±0.22	0.42
r'20 (mV)	0.28±0.10	0.23±0.11	0.03	0.32±0.15	0.22±0.11	<0.01
r'40 (mV)	0.22±0.07	0.18±0.08	0.02	0.21±0.08	0.15±0.07	<0.01
r'-r'20 (mV)	0.10±0.08	0.19±0.13	<0.001	0.18±0.12	0.31±0.16	<0.01
r'-r'40 (mV)	0.16±0.11	0.25±0.18	0.02	0.29±0.19	0.38±0.23	0.15
STb (mV)	0.18±0.07	0.17±0.08	0.31	0.14±0.06	0.12±0.07	0.09
r'-STb (mV)	0.20±0.13	0.25±0.18	0.27	0.36±0.24	0.41±0.24	0.27
DR20	0.24±0.14	0.43±0.15	<0.0001	0.34±0.14	0.57±0.16	<0.0001
DR20-STb	0.50±0.11	0.80±0.12	<0.0001	0.51±0.12	0.78±0.12	<0.0001

Significant at 0.05 level.
V2ic3, V2 at the third intercostal space; HR, heart rate; r', amplitude of the peak of r' wave; r'20, r'40, amplitudes of ST-segment 20 ms and 40 ms after the r' wave; r'-r'20, r'-r'40, r'-STb, differences in amplitudes between r' and r'20, r' and r'40, and r' and STb, respectively; STb, amplitude of the bottom of the ST-segment; DR20, DR20-STb, rate of descent of the ST-segment (r'-r'20/r' and r'-r'20/r'-STb, respectively).

a) positive responder

b) negative responder

Figure 2. Representative ECGs of positive and negative responders in lead V2ic3. QRS duration, r', r'20, r'40, r'-r'20, DR20, and DR20-STb were 93 ms, 0.42 mV, 0.30 mV, 0.12 mV, 0.29, and 0.47, respectively, in the positive responder (a), and 94 ms, 0.42 mV, 0.19 mV, 0.16 mV, 0.23 mV, 0.55, and 0.92, respectively, in the negative responder (b). V2ic3; V2 at the third intercostal space. Other abbreviations as Figure 1.

NR), larger value of r'20 and r'40 (0.28±0.10 vs 0.23±0.11 mV; P=0.03, 0.22±0.07 vs 0.18±0.08 mV; P=0.02, PR vs NR, respectively), and significantly smaller value of r'-r'20, r'-r'40, DR20, and DR20-STb (0.10±0.08 vs 0.19±0.13 mV; P<0.001, 0.16±0.11 vs 0.25±0.18 mV; P=0.02, 0.24±0.14 vs 0.43±0.15; P<0.0001, 0.50±0.11 vs 0.80±0.12; P<0.0001, PR vs NR, respectively). Neither r' nor STb differed significantly between the 2 groups (**Table 2**). Moreover, in lead V2ic3, similar results are obtained (**Table 2**). Representative ECGs are shown in **Figure 2**. The S wave duration in lead II and the difference between QRSv2 and QRSv5 (QRSv2-QRSv5), were not significantly different between PR and NR (30.4±20.5 vs 35.9±18.6 ms; P=0.59, -5.8±8.9 vs -7.4±12.1 ms; P=1.00, PR vs NR, respectively).

Of these parameters, DR20 and DR20-STb in leads V2 and V2ic3 differed most significantly between the 2 groups

(**Figure 3**). We plotted receiver operating characteristic curves for these parameters, and determined the point exhibiting the highest sensitivity and specificity. Sensitivity, specificity, PPV, and NPV using these parameters with the best cut-off point are shown in **Table 3**. All of the 4 parameters could predict the test outcome well. In particular, DR20-STb in lead V2ic3 was the most useful predictor in these parameters. When 'DR20-STb in lead V2ic3 <0.62' was tested as a predictor of positive outcome, parameters for the prediction of positive outcome on drug testing were as follows: sensitivity 85.7%, specificity 90.0%, PPV 92.3%, and NPV 81.8%.

Discussion

In the present study, we evaluated the differences in baseline ECG characteristics between PR and NR in individuals

Figure 3. Comparison of DR20 and DR20-ST_b values in leads V2 and V2_{ic3} between PR and NR. DR20 and DR20-ST_b in leads V2 and V2_{ic3} were significantly different between the 2 groups ($P < 0.0001$). PR, positive responders; NR, negative responders. Other abbreviations as Figure 1.

Table 3. Parameters for the Prediction of Positive Outcome on Drug Provocation Testing

Parameters	Cut-off	Sensitivity	Specificity	PPV	NPV
DR20 (V2)	<0.35	80.0	82.6	87.5	73.1
DR20-ST _b (V2)	<0.63	77.1	82.6	87.1	70.4
DR20 (V2 _{ic3})	<0.47	82.1	80.0	85.2	76.2
DR20-ST _b (V2 _{ic3})	<0.62	85.7	90.0	92.3	81.8
	<0.60	82.1	100.0	100.0	80.0

PPV, positive predictive value; NPV, negative predictive value; V2_{ic3}, V2 at the third intercostal space.

with SB-ECG on drug provocation testing. The results of the present study show that DR20 and DR20-ST_b in leads V2 and V2_{ic3} are useful non-invasive predictors of positive outcome on drug testing.

We showed the values of QRS duration, r'^{20} , and r'^{40} were significantly larger and those of $r'-r'^{20}$, DR20, and DR20-ST_b were significantly smaller in PR, compared with those in NR. DR20 and DR20-ST_b, in particular, differed most significantly between the 2 groups. These findings indicate that PR with SB-ECG exhibited a 'gradually' descending ST-segment, like type 1 ECG, on the baseline ECG. The cellular mechanism of type 1 ECG has been found to involve the following: incomplete depolarization during phase 0 produces a deep notch in phase 1 of the epicardial action potential, which augments a transmural current from the endocardium and creates a prominent J point (ST-segment) elevation. The subsequent dome produces an attenuated transmural current flow that contributes to a downslope (coved-type) of the ST segment.^{20–23} We speculate that PR with SB-ECG might have the same electrophysiological characteristics, arising slowly from a deep notch in phase 1 of epicardial action potential as patients with type 1 ECG, and manifest some of them on the baseline ECG.

In this study, DR20 and DR20-ST_b in lead V2 and V2_{ic3} could predict the test outcome well. In particular, DR20-ST_b in lead V2_{ic3} was the most useful predictor in these

parameters. Some previous studies have shown that the ECG recorded at a higher intercostal space is more useful for the diagnosis of Brugada syndrome than that recorded at standard position.^{14–19} In the present study, we support the usefulness of the ECG at the third intercostal space to evaluate predictors of PR on the drug testing.

Several predictors of positive testing have been reported. Meregalli et al reported the QRS duration, the J-point elevation (leads V1, V2, V1_{ic3}, and V2_{ic3}), and the S wave duration in lead II on baseline ECG were significantly different between PR and NR. However, they failed to predict the outcome of testing, using these parameters.¹¹ In the present study, only QRS duration in leads V2 and V2_{ic3} was significantly different between PR and NR, while r' in leads V2 and V2_{ic3}, and the S wave duration in lead II were not significantly different. Nakazawa et al reported that the difference of the QRS duration between in leads V2 and V5 (QRS_{V2}-QRS_{V5}) ≥ 0 ms was found to be a predictor of positive drug provocation test.¹² In the current study, however, this predictor was not significantly different between the 2 groups. Hermida et al reported that baseline J wave elevation >0.16 mV in lead V2 at the second intercostal space had a specificity of 100%, a sensitivity of 40%, a PPV of 100% and a NPV of 28%.¹³ Comparing these reports, DR20 and DR20-ST_b in lead V2 and V2_{ic3} in the present study are better predictors of positive drug testing.

The non-invasive ECG parameters, DR20 and DR20-ST_b

in leads V2 and V2ic3, might be useful for distinguishing PR from NR on drug provocation testing. These ECG parameters might make drug provocation testing unnecessary for unmasking a type 1 ECG, and consequently avoid the risk of drug-induced ventricular tachyarrhythmias. Moreover, we could discriminate non-invasively the patients with arrhythmogenic substrate in Brugada Syndrome from the individuals without it.

The present study has several limitations. First, DR20 or DR20-STb was calculated with r' , $r'20$, and STb. However, the visual measurement of $r'20$ on the ECG at a speed of 25 mm/s is difficult. In this study, we magnified the ECGs and measured with a CardioLab system as digital data. For measurement of $r'20$ using a standard ECG recording system, it might be necessary to record at a high paper speed and use magnification. If these parameters can be measured in an automated ECG analysis system, these might be more useful in the clinical setting. Second, it is known that the electrocardiographic features of Brugada syndrome are dynamic and often concealed.^{24,25} Therefore, judgment regarding the presence of this syndrome with the ECG at a single recording is likely to underestimate the diagnosis of it. It might be necessary to record ECGs repeatedly in the same individuals for evaluation of this matter. Third, it has been known that some individuals showed type 1 ECG only in the higher intercostal space on drug testing. However, it is still controversial whether the results of testing should be judged by the ECG involving in the higher intercostal space, because of concern about false-positive results as the recent consensus report showed.² Therefore, we defined the positive response as the occurrence of type 1 ECG only at the standard position. Finally, the present study is retrospective evaluation. Therefore, further prospective study is needed to assess the usefulness of these non-invasive ECG parameters as predictors of positive drug provocation test.

Conclusion

In individuals with saddle-back type ST-segment elevation, DR20 and DR20-STb in leads V2 and V2ic3 might be useful as non-invasive predictors of positive pilsicainide testing. These parameters could discriminate the patients with arrhythmogenic substrate in Brugada syndrome from the individuals without it.

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