Vagal response is involved in the occurrence of ventricular fibrillation in patients with early repolarization syndrome

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BACKGROUND Patients with early repolarization syndrome (ERS) and Brugada syndrome (BruS) have comparable clinical symptoms. In both conditions, ventricular fibrillation (VF) is experienced often near midnight or in the early morning hours when the parasympathetic tone is augmented. However, differences between ERS and BruS regarding the risk of VF occurrence have recently been reported. The role of vagal activity remains especially unclear.

OBJECTIVE The goal of this study was to determine the relationship between VF occurrence and autonomic nervous activity in patients with ERS and BruS.

METHODS We enrolled 50 patients with ERS (n = 16) and BruS (n = 34) who received an implantable cardioverter-defibrillator. Of these, 20 patients (5 ERS and 15 BruS) experienced VF recurrence (recurrent VF group). We investigated baroreflex sensitivity (BaReS) with the phenylephrine method and heart rate variability using Holter electrocardiography in all patients to estimate autonomic nervous function.

RESULTS In both patients with ERS and BruS, there was no significant difference in heart rate variability between the recurrent VF and nonrecurrent VF groups. However, in patients with ERS, BaReS was significantly higher in the recurrent VF group than in the nonrecurrent VF group ($P = .03$); this difference was not evident in patients with BruS. High BaReS was independently associated with VF recurrence in patients with ERS according to Cox proportional hazards regression analyses (hazard ratio 1.52; 95% confidence interval 1.031–3.061; $P = .032$).

CONCLUSION Our findings suggest that in patients with ERS, an exaggerated vagal response, as represented by increased BaReS indices, may be involved in the risk of VF occurrence.

KEYWORDS Baroreflex sensitivity; Brugada syndrome; Early repolarization syndrome; Parasympathetic nerve activity; Ventricular fibrillation

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Introduction

Early repolarization (ER) pattern on 12-lead electrocardiography (ECG) was previously thought to be of no pathological significance. Later, however, a link between the ER pattern and the onset of ventricular fibrillation (VF) has been identified. In 2008, Haïssaguerre et al[1] reported cases of early repolarization syndrome (ERS) associated with VF and proposed the disease concept of ERS. In contrast, several studies linking ER patterns to the incidence of sudden cardiac death (SCD) have found that the vast majority of subjects with an ER pattern, discovered by chance during physical examinations, remain asymptomatic and arrhythmic events and SCD occur in only a small minority of patients (~1:10,000).[2] Risk stratification is notoriously difficult in such patients. In addition, Mahida et al[3] reported that electrophysiology studies were not useful for risk stratification in patients with ERS. As a result, more precise risk stratification tools remain a clinical need and challenge.

The clinical presentation of patients with ERS is similar to that of patients with Brugada syndrome (BruS) at least in part.[1] VF is more common in both conditions around midnight or early in the morning when the heart rate is slower and parasympathetic tone is increased. Therefore, it has been proposed to combine the ERS and BruS categories into a single diagnosis, J-wave syndrome (JWS).[4]

The baroreflex sensitivity (BaReS) test has been used to assess the activity of cardiovascular autonomic nerves; BaReS is thought to reflect the tone and reactivity of the parasympathetic nervous system. As a result, BaReS can be used

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to identify patients at high risk of life-threatening ventricular tachyarrhythmia and SCD after myocardial infarction.[5,6] We previously investigated and reported on the relationship between autonomic function and the risk of VF occurrence in patients with ERS and BruS referred to as JWS.[7] However, it has recently been reported that there are some differences in the risk of VF occurrence between ERS and BruS[4,8] and thus the risk of VF may differ between patients with ERS and BruS. We concentrated on the differences in reflex vagal activity in this regard.

The goals of this study were to determine the relationship between autonomic activity and the risk of VF in patients with ERS and BruS and to assess the utility of measuring vagal responses.

Methods

Study population

Between June 2000 and May 2022, 50 consecutive patients with ERS (n = 16; mean age 46 ± 17 years) and BruS (n = 34; mean age 49 ± 14 years) had implantable cardioverter-defibrillator (ICD) implanted for spontaneous VF or syncope possibly due to VF. All patients were diagnosed with either ERS or BruS according to the 2016 expert consensus conference report.[4] Data for 28 of these patients, which were enrolled before December 2014, were included in the previous publication.[7] We included 22 additional patients to the cohort of the previous publication for the present study. All 34 patients with BruS had a coved-type (type 1) ST-segement elevation (Figure 1A), either spontaneously or after class I antiarrhythmic drug provocation (pilsicainide [1 mg/kg body weight] at 10 mg/min, intravenously).[9] J waves were accentuated only in the inferior and/or lateral leads of patients with ERS (Figure 1B). All patients with ERS underwent a provocation test with a class I antiarrhythmic drug; none exhibited coved-type ST-segment elevation in the right precordial leads. The *ER pattern* was defined as a "notch" or "slur" with an amplitude of ≥0.1 mV on the terminal QRS portion.[4,10] The J-wave amplitude was measured in notch morphology at the peak of the positive deflection, relative to QRS onset. The J-wave amplitude was measured at the inflection point of the QRS complex relative to QRS onset in slur morphology. According to the lead electrodes, the *region of the ER pattern* was defined as the inferior leads (II, III, and aVF) and the lateral leads (I, aVL, and V_4–V_6). If an ER pattern was observed in both regions, it was considered to be "extensive J-point elevation." When 2 of the following criteria were met, late potentials on signal-averaged ECGs were defined as positive: (1) filtered QRS duration >105 ms, (2) root mean square voltage of signals in the last 40 ms of the total filtered QRS complex <15 μV, and (3) duration of low-amplitude signals (<40 μV) of the filtered QRS complex >39 ms. Physical examination, chest radiography, 12-lead ECG, echocardiography, treadmill exercise ECG, and coronary angiography all revealed that no patient had organic heart disease (including the coronary spasm provocation test). No patient took medications that influence the function of the autonomic nervous system. All patients were followed up at Oita University Hospital. Patients were seen every 3–6 months for clinical review and device monitoring. The follow-up period lasted 75.6 ± 65.1 months.

BaReS measurements

For BaReS assessments, all subjects were studied while lying supine in a quiet room between 9 and 11 AM.[11] A catheter was inserted into the right cubital vein, and noninvasive tonometry was used to measure arterial blood pressure (Jentow-7700, Nihon Colin, Hiroshima, Japan) (Figure 2A). Arterial blood pressure and a 12-lead ECG were monitored simultaneously. The data were saved in a pulse code modulation data recorder (RD-200T, TEAC, Tokyo, Japan). After a 30-minute break to allow vital signs to stabilize, the patient was instructed to breathe at a rate of 15 breaths/min (measured using a metronome). The phenylephrine method was used to assess BaReS. Phenylephrine (2–3 μg/kg) was injected over 15 seconds to increase systolic

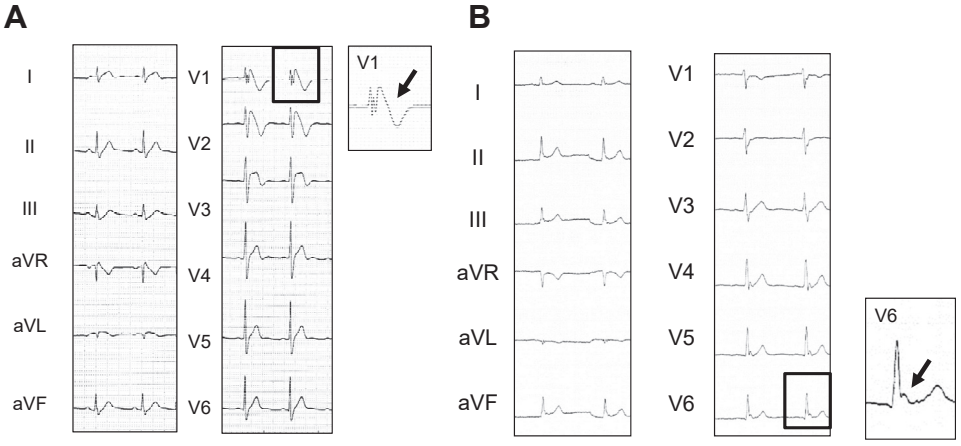

Figure 1 Representative 12-lead electrocardiograms for patients with Brugada syndrome and early repolarization syndrome (ERS). **A:** Twelve-lead electrocardiogram for a patient with Brugada syndrome. The *arrow* indicates coved-type ST-segment elevation. **B:** Twelve-lead electrocardiogram for a patient with ERS. The *arrow* indicates an augmentation of the J wave with notch type.

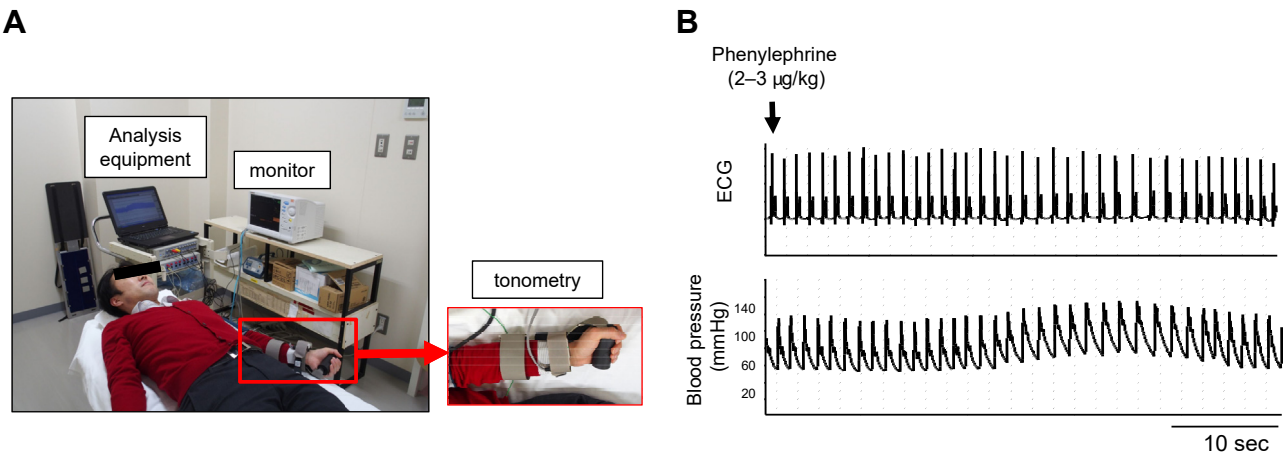

Figure 2 Baroreflex sensitivity (BaReS) measurement methods. **A:** A picture of a healthy volunteer during BaReS measurement. **B:** A representative record of the electrocardiogram (ECG) and blood pressure after intravenous phenylephrine administration.

blood pressure by 15–40 mm Hg (Figure 2B).[5] BaReS was calculated as the slope of the linear regression line, relating changes in systolic blood pressure to changes in RR interval. Regression lines with >20 data points and a correlation coefficient (r) of >0.8 have been used for analyses.[5] BaReS assessments were conducted during the hospital stay for ICD implantation. In most cases, the assessments were conducted after ICD implantation and before discharge.

Heart rate variability

Heart rate variability (HRV) was measured using Holter ECG recordings over 24 hours (Marquette Electronics, Milwaukee, WI). The RR interval's power spectrum was computed using a fast Fourier transform algorithm and expressed as the area under the power spectrum. The power of 2 spectral bands was calculated: the low-frequency (LF) component at 0.04–0.15 Hz and the high-frequency (HF) component at 0.15–0.40 Hz. Because the distribution of the measured HRV values was skewed, they were transformed using the natural logarithm. The LF/HF ratio was also computed.

Statistical analyses

Data are expressed as mean ± SD for continuous variables or as number and percentage for categorical variables. To determine whether continuous variables were normally distributed, the Shapiro-Wilk test was used. The Student t test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used to compare non-normally distributed continuous variables. The χ^2 test was used for categorical variables. The Kaplan-Meier method was used to create event-free curves between the high BaReS group and the non-high BaReS group, which were then compared using the log-rank test. Using receiver operating characteristic curves, the high or low BaReS group was determined. A multivariate Cox proportional hazards regression analysis was performed using several commonly reported risk factors to identify independent predictors of the prevalence of VF in patients with ERS. A P value of <.05 was considered significant. All computations were carried out using JMP v.13.2.1 software (SAS Institute Inc, Cary, NC).

The Oita University Faculty of Medicine Ethics Committee approved this study. Written informed consent was obtained from each patient. The research was conducted according to the guidelines outlined in the Helsinki Declaration.

Results

Patient characteristics

The clinical characteristics of 16 patients with ERS and 34 patients with BruS are summarized in Table 1. All 50 patients were implanted with an ICD after experiencing spontaneous VF (n = 37) or syncope caused by VF (n = 13). The proportion of patients with documented VF before ICD implantation was significantly higher in patients with ERS than in

Table 1 Characteristics of patients with BruS and ERS

Characteristic	ERS (n = 16)	BruS (n = 34)	P
Male	15 (94)	33 (97)	.58
Age (y)	46 ± 17	49 ± 15	.54
Family history of SCD	0 (0)	1 (3)	.49
Heart rate (beats/min)	70 ± 15	73 ± 9	.34
Documented VF	15 (94)	22 (65)	.03*
Positive late potential	5 (31)	25 (76)	.003†
BaReS (ms/mm Hg)	9.2 ± 2.9	7.8 ± 4.3	.25
HF power (ln(ms^2))	7.5 ± 3.5	6.7 ± 1.9	.10
LF/HF	2.4 ± 1.7	2.7 ± 1.3	.13
VF recurrence after ICD implantation	5 (31)	15 (44)	.39
Follow-up period (mo)	79.0 ± 54.2	74.9 ± 70.7	.84

Values are presented as mean ± SD or n (%).

BaReS = baroreflex sensitivity; BruS = Brugada syndrome; ERS = early repolarization syndrome; HF = high frequency; ICD = implantable cardioverter-defibrillator; LF = low frequency; SCD = sudden cardiac death; VF = ventricular fibrillation.

*P < .05.

†P < .01.

patients with BruS (P = .03). Furthermore, patients with BruS exhibited significantly higher positive late potentials than did patients with ERS (P = .003). There was no significant difference between patients with ERS and BruS in any clinical factor, including BaReS indices and HRV indices (Table 1).

Clinical differences in VF recurrence between patients with ERS and BruS

VF recurrence occurred in 5 patients with ERS (31%) and 15 patients with BruS (44%), 27.4 ± 33.7 months after ICD implantation. BaReS was significantly higher in the recurrent VF group than in the nonrecurrent VF group in patients with ERS (P = .03) (Figure 3). Conversely, in patients with BruS, BaReS tended to be higher in the recurrent VF group than in the nonrecurrent VF group, but the difference was not statistically significant (P = .11). There was no significant difference in any other factor between the 2 groups of patients with ERS and BruS (Table 2).

Recurrence-free VF

In patients with ERS, we investigated the relationship between VF recurrence risk and BaReS indices. BaReS cutoff indices were determined from the receiver operating characteristic curve; the BaReS index with the highest sensitivity and specificity for the prediction of VF recurrence was 10.0 ms/mm Hg (sensitivity 0.80; specificity 0.82). Therefore, we defined "high BaReS" as a BaReS index of ≥10.0 ms/mm Hg. We divided patients into 2 groups on the basis of BaReS indices: The values for the high BaReS group (n = 6) and the non-high BaReS group (n = 10) were 12.2 ± 2.1 and 7.3 ± 1.3 ms/mm Hg, respectively. The high BaReS group (n = 4 [67%]) had more VF recurrences than did the non-high BaReS group (n = 1 [10%]) (P = .018). Kaplan-Meier analyses revealed that recurrence-free VF was significantly lower in the high BaReS group than in the non-high BaReS group (P = .008) (Figure 4).

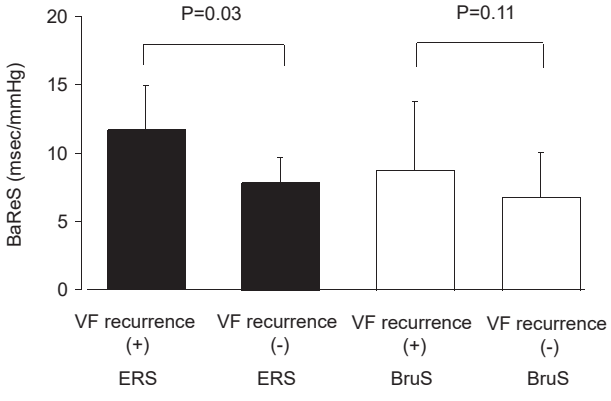

Figure 3 Baroreflex sensitivity (BaReS) assessment for the nonrecurrent ventricular fibrillation (VF) group and recurrent VF group in patients with early repolarization syndrome (ERS) and Brugada syndrome (BruS). In patients with ERS, BaReS was significantly higher in the recurrent VF group than in the nonrecurrent VF group (P = .03). In patients with BruS, BaReS tended to be higher in the recurrent VF group than in the nonrecurrent VF group, but the difference was not statistically significant (P = .11).

Multivariate predictors of VF recurrence

Multivariate Cox proportional hazards regression analyses of VF recurrence are presented in Table 3. In addition to BaReS indices, we performed multivariate analyses on J-wave amplitude and the presence of extensive J-point elevation, both of which are commonly reported risk factors in patients with ERS. These data suggest that the BaReS index predicts VF recurrence independently (hazard ratio 1.52; 95% confidence interval 1.031–3.061; P = .032). The hazard of VF recurrence increased by 52% per 1 ms/mm Hg in BaReS index.

Discussion

The following were the main findings of the present study: (1) BaReS indices and HRV estimated with Holter ECG recordings were not significantly different between patients with ERS and BruS; (2) HRV was not significantly different between those with and without recurrent VF in both patients with ERS and patients with BruS; and (3) BaReS was significantly higher in the recurrent VF group than in the nonrecurrent VF group in patients with ERS but not in patients with BruS. In addition, in patients with ERS, BaReS could predict VF recurrence independently. Our findings suggest that the vagal response (as represented by an increased BaReS index) may be responsible for the occurrence of VF in patients with ERS. This is the first report of a link between the vagal response and the occurrence of VF in patients with ERS.

In patients with ERS with a history of VF, the recurrence rate of VF has been reported to be 41% at 5-year follow-up.[1] As a result, even after ICD implantation, recurrent VF in patients with ERS remains a serious problem. In addition to drug therapy such as quinidine,[1] the effectiveness of catheter ablation for the prevention of VF recurrence has recently been reported.[12] To determine the indications for these treatments, the risk stratification of VF recurrence in patients with ERS is an urgent issue.

ERS and autonomic nervous function

The electrophysiological basis of the J wave in patients with ERS is likely to be a prominent instant outward K^+ channel current (I_{to})-mediated spike and dome action potential in the ventricular epicardium rather than the endocardium.[13] It has been reported that autonomic nervous activity is involved in the augmentation of the J wave and VF occurrence in patients with JWS (including ERS and BruS).[1,7,14,15] Koncz et al[16] demonstrated that acetylcholine is capable of directly causing VF in the experimental models of ERS. Furthermore, acetylcholine, a parasympathetic neurotransmitter, activates small conductance calcium-activated potassium current, which induces J-wave augmentation and facilitates the induction of ventricular arrhythmias according to Fei et al.[17] Abe et al[18] reported that J-point amplitude was strongly associated with HF components on Holter ECG recordings in patients

Table 2 Characteristics of patients with and without recurrence of VF

Characteristic	ERS (n = 16)			BruS (n = 34)		
	VF recurrence (+) (n = 5)	VF recurrence (−) (n = 11)	*P*	VF recurrence (+) (n = 15)	VF recurrence (−) (n = 19)	*P*
Male	5 (100)	10 (91)	.49	15 (100)	18 (95)	.37
Age (y)	39 ± 17	48 ± 17	.36	45 ± 15	51 ± 14	.23
Family history of SCD	0 (0)	0 (0)	–	0 (0)	1 (5)	.37
Heart rate (beats/min)	80 ± 19	65 ± 12	.16	74 ± 9	72 ± 9	.61
Documented VF	5 (100)	10 (91)	.49	12 (80)	10 (53)	.10
Positive late potential	2 (40)	3 (27)	.61	12 (80)	13 (68)	.45
BaReS (ms/mm Hg)	11.8 ± 3.3	8.0 ± 1.9	.03*	9.0 ± 5.2	6.9 ± 3.4	.24
HF power (ln(ms^2))	7.5 ± 3.7	7.5 ± 3.7	>.99	7.0 ± 2.1	6.5 ± 1.8	.64
LF/HF	2.3 ± 1.0	2.4 ± 2.0	.69	2.9 ± 1.3	2.6 ± 1.4	.42

Values are presented as mean ± SD or n (%).

BaReS = baroreflex sensitivity; BruS = Brugada syndrome; ERS = early repolarization syndrome; HF = high frequency; LF = low frequency; SCD = sudden cardiac death; VF = ventricular fibrillation.

*$P < .05$.

with idiopathic VF. Furthermore, Mizumaki et al[19] found that the slope of the J-wave amplitude/HF component in patients with idiopathic VF was significantly steeper than in control patients. These findings suggest that increased vagal tone plays a significant role in the occurrence of VF in patients with JWS. Previously, we demonstrated that propranolol and verapamil enhance J waves while isoproterenol or disopyramide suppress J waves in a patient with ERS.[20] J-wave augmentation may result from a decrease in inward calcium current and an increase in I_{to} as a result of a decrease in heart rate. In contrast, J-wave suppression may occur as a result of an increase in inward calcium current and a decrease in I_{to} caused by tachycardia or the anticholinergic effect of disopyramide.

We estimated vagal nerve activity in this study using 2 methods: HRV (with Holter ECG recordings) and BaReS (using the phenylephrine method). The findings showed that HRV indices (including HF power and LF/HF as determined by Holter ECG recordings) were not involved in the occurrence of VF in patients with ERS. In contrast, BaReS was involved in the occurrence of VF. Unlike steady vagal power, BaReS using the phenylephrine method can be used to estimate the reflex reactivity of parasympathetic nerves. The parasympathetic nerve activity plays an important role in the occurrence of VF, and our results indicate that parasympathetic nerve reflex reactivity is more important than tonic vagal power in patients with ERS. However, a larger multicenter study is needed to elucidate our findings. Another possibility may be that owing to differences in reproducibility, BaReS using the phenylephrine method may give a more accurate estimate of vagal activity than does the Holter ECG test. In other words, because HRV is more susceptible to diurnal and daily variations, Holter ECG testing may be less reproducible than BaReS testing.

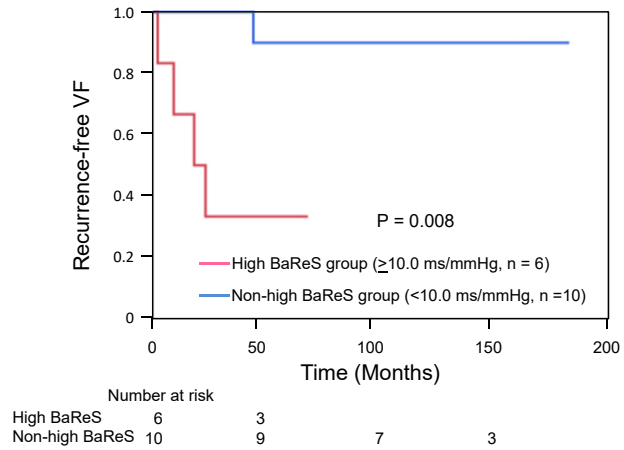

Figure 4 Kaplan-Meier event-free curves for ventricular fibrillation (VF) recurrence vs baroreflex sensitivity (BaReS) index in patients with early repolarization syndrome. A BaReS index of ≥10.0 ms/mm Hg is defined as "high BaReS," allowing patients to be divided into 2 groups. Recurrence-free VF as evaluated by Kaplan-Meier analyses was significantly lower in the high BaReS group than in the non-high BaReS group ($P = .008$).

Risk stratification for VF occurrence in patients with ERS

Patients with ERS with a history of VF are more likely to develop VF than did subjects with an ER pattern but no history of VF. Therefore, ICD implantation is recommended for patients with ERS with a history of VF.[4] The following findings on 12-lead ECG indicated a high risk of VF occurrence: (1) extensive J-point elevation in both inferior and lateral

Table 3 Multivariate predictors of VF recurrence

Variable	Multivariate HR	95% CI	*P*
Extensive J-point elevation at the inferior and lateral ECG leads	0.45	0.034–5.070	.495
J-wave amplitude (mV)	0.60	0.052–2.339	.532
BaReS (ms/mm Hg)	1.52	1.031–3.061	.032*

BaReS = baroreflex sensitivity; CI = confidence interval; ECG = electrocardiographic; HR = hazard ratio; VF = ventricular fibrillation.

*$P < .05$.

ECG leads,[21] (2) excessive J-point elevation ≥0.2 mV,[22] (3) horizontal or descending ST segment after J-point elevation,[23] and (4) J-wave findings with significant diurnal or daily variations.[4] Furthermore, Kamakura et al[24] reported that VF recurrence was significantly more common in 12 patients with saddleback-type ST elevation on the right precordial leads among 31 patients with ERS with a history of VF. In contrast, EPS is reportedly ineffective in assessing the risk of VF recurrence in patients with ERS despite its utility for risk stratification in patients with BruS.[3] The risk stratification for VF recurrence in patients with ERS is still unsatisfactory. The BaReS index was found to be one of the most useful tools for risk stratification in patients with ERS in this study.

Differences between patients with ERS and BruS

In a previous study, we found that idiopathic VF patients' J-wave amplitudes on Holter ECG recordings were more significantly connected with vagal activity (HF) than controls.[25] We then studied the relationship between VF occurrence and autonomic nerve function in patients with JWS.[7] The findings showed that HF power and LF/HF determined from Holter ECG recordings, the 2 HRV indices, were not related to the occurrence of VF in patients with JWS. In contrast, BaReS contributed to the occurrence of VF.

Traditionally, ERS and BruS were thought to have many similarities, but recent data indicate that they differ in various respects.[4] Differences between these syndromes include the following: (1) the region of the heart most affected (right ventricular outflow tract vs inferior left ventricle), (2) the incidence of late potentials in signal-averaged ECGs,[26] (3) sodium channel blockers heighten the J wave in the right precordial leads in patients with BruS but reduce the J wave in inferolateral leads in patients with ERS,[26] and (4) the higher prevalence of atrial fibrillation in BruS than in ERS.[27] Although the depolarization abnormality theory has recently been put forth on the basis of a variety of epicardial mapping findings, the repolarization abnormality theory has historically been proposed as the cause of BruS.[28] In our study, patients with BruS had significantly more positive late potentials than did those with ERS, representing either a conduction disorder or an advanced stage of repolarization abnormality. Although late potentials are traditionally attributed to conduction delay, it should be acknowledged that repolarization abnormalities can equally manifest as late potentials in the experimental settings of JWSs.[29] The present study demonstrates that vagal response activity was involved in VF occurrences in patients with ERS, but not in patients with BruS. Although we are unable to explain the precise mechanism, we hypothesize that it may be caused by variations in the degree to which repolarization anomalies are involved in the onset of VF. To better understand this mechanism, more thorough research is required.

Limitations

The present study had several limitations. First, the number of patients enrolled was small, with only 16 patients with ERS and 34 patients with BruS, and the average follow-up period for both of them is short. In particular, the number of patients with ERS with recurrent VF is extremely small (n = 5). Therefore, we cannot rule out the possibility that the result is a type II error. Additionally, only individuals with a history of VF or syncope that may have been caused by VF were allowed to participate in this retrospective single-center study. As a result, bias in patient selection may exist. There are many asymptomatic people with ER patterns who have positive results[2]; hence, accurate risk stratification is difficult and still not possible. To accurately quantify the likelihood of VF incidence in patients with ERS, large prospective multicenter studies encompassing asymptomatic patients with ERS must be conducted in the future. In addition, the same applies to asymptomatic patients with BruS. Second, ECG patterns for patients with ERS typically vary daily. In the present study, we did record multiple Holter ECGs. Therefore, we cannot completely rule out the potential that the Holter ECG test might have produced different results had it been conducted on a different day. Third, even if BaReS is assessed with phenylephrine infusion, it may not be fully reproducible with respect to autonomic nervous activity and may need to be evaluated again on another day. A controlled-breathing procedure, however, reportedly has good reproducibility.[30] By having patients breathe at a rate of 15 breaths/min while using a metronome, we anticipate that the best reproducibility was attained. Nevertheless, because the BaReS assessments were not conducted immediately before the VF episode, we cannot rule out the possibility that the patient's BaReS is not truly associated with VF recurrence.

Conclusion

Our results suggest that the involvement of vagal nerve activity in VF occurrence differs between patients with ERS and BruS. The BaReS index, which measures vagal response activity in patients with ERS and represents it, may be one of the helpful tools for predicting the likelihood of developing VF.

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