Table 2 Clinical characteristics and electrophysiological findings of the subjects.

	Brugada group ($n=45$)				Non-Brugada group ($n=32$)			
	Symptom[a] n (%) $n=8$	Syncope[a] n (%) $n=9$	Asymptom[a] n (%) $n=28$	Test for intra-group (p)	Symptom[a] n (%) $n=7$	Syncope[a] n (%) $n=13$	Asymptom[a] n (%) $n=12$	Test for intra-group (p)
Type 1 ECG in control	5 (56)	3 (33)	12 (43)	0.46	0 (0)	0 (0)	0 (0)	–
Types 1–3 ECG in control	6 (75)	4(44)	17 (61)	0.44	1 (14)	1 (8)	3 (25)	0.49
Type 1 ECG after pilsicainide test	8 (100)	9 (100)	28 (100)	–	0 (0)	0 (0)	0 (0)	–
Types 1–3 ECG after pilsicainide test	8 (100)	9 (100)	28 (100)	–	1(14)	3 (23)	3 (25)	0.85
MaxΔST elevation ($\geqq$200 μV)	6 (75)	8 (89)	24 (86)	0.70	0 (0)	0 (0)	0 (0)	–
Positive in late potential	6 (75)	7 (78)	16 (58)	0.31	1 (14)	4 (31)	3 (25)	0.70
ERP								
RV apex at BCL 600 ms (ms)	247 $\pm$ 6	233 $\pm$ 13	241 $\pm$ 14	0.21	246 $\pm$ 24	244 $\pm$ 17	244 $\pm$ 21	0.98
RV apex at BCL 400 ms (ms)	230 $\pm$ 10	210 $\pm$ 8	221 $\pm$ 11	0.02	222 $\pm$ 19	224 $\pm$ 16	219 $\pm$ 22	0.82
RV outflow tract at BCL 600 ms (ms)	237 $\pm$ 15	228 $\pm$ 17	235 $\pm$ 11	0.43	255 $\pm$ 31	243 $\pm$ 18	236 $\pm$ 18	0.35
RV outflow tract at BCL 400 ms (ms)	237 $\pm$ 12	211 $\pm$ 16	225 $\pm$ 15	0.05	225 $\pm$ 31	225 $\pm$ 18	227 $\pm$ 20	0.96
Induction of VF	8 (100)	8 (89)	17 (60)	0.04	1 (14)	3 (23)	0 (0)	0.22

There was no significant difference in ERP in the RV apex or in the RV outflow at BCLs 600 and 400 ms between the Brugada group and the non-Brugada group. Types 1–3 ECG: the repolarization pattern of type 1, type 2, or type 3 was shown in ECG. Asymptom, asymptomatic; ECG, electrocardiogram; ERP, effective refractory period; RV, right ventricle; BCL, basic cycle length; VF, ventricular fibrillation.

[a] Subgroup.

Table 3 Incidence and univariate analysis for the induction of ventricular fibrillation in the control study.

Variables	n	Incidence	Univariate analysis		
		Number of patients with induced VF (%)	OR	95% Confidence intervals	p
Symptoms	15	10 (67)	2.28	0.70–7.43	0.173
Syncope	22	11 (50)	0.96	0.36–2.59	0.943
Family history	13	8 (62)	1.70	0.50–5.77	0.392
Type 1 ECG in control	20	16 (80)	5.91	1.75–19.96	0.004
Positive in late potential	37	25 (68)	3.87	1.50–9.97	0.005
Type 1 ECG after pilsicainide test	45	34 (76)	16.69	5.17–53.87	0.0001
MaxΔST elevation (≧200 μV)	38	30 (79)	12.50	4.25–36.75	0.0001

Symptoms: documented VF and/or aborted sudden cardiac death; syncope: syncope from unknown etiology; VF, ventricular fibrillation; OR, Mantel-Haenszel odds ratio; ECG, electrocardiogram.

Electrophysiological stimulation test in subjects in the control state

EPS was performed in all subjects. There was no significant difference of the ERP in the RV apex at BCL 600 ms (239 ± 13 ms vs. 245 ± 20 ms) and 400 ms (220 ± 14 ms vs. 220 ± 17 ms) between the Brugada group and non-Brugada group. Furthermore, there was no significant difference in the ERP in the RV outflow tract at BCL 600 ms (234 ± 15 ms vs. 242 ± 20 ms) and 400 ms (222 ± 17 ms vs. 226 ± 20 ms) between the Brugada group and non-Brugada group. There was no significant difference in the ERP in the RV apex and RV outflow tract at BCL 600 and 400 ms among the subgroups of the Brugada group as well as those of the non-Brugada group (Table 2).

Induction of VF. VF was induced in 73% (33/45) of patients in the Brugada group and 13% (4/32) of patients in non-Brugada group. Inducibility of VF was significantly ($p < 0.0001$) higher in Brugada syndrome than non-Brugada syndrome.

In the Brugada group with induction of VF ($n = 33$), VFs were induced by single ventricular extrastimuli ($n = 0$, 0%) and double ventricular extrastimuli ($n = 15$, 45%) from RV apex and/or RV outflow tract. Further, VFs were induced by triple ventricular extrastimuli ($n = 18$, 55%). VFs were more frequently ($p = 0.009$) induced by pacing from RV outflow tract ($n = 27$, 82%) than from RV apex ($n = 17$, 52%) and they were induced by triple ventricular extrastimuli from both pacing sites ($n = 11$, 33%).

In the non-Brugada group with induction of VF ($n = 4$), VFs were induced by single ventricular extrastimulation ($n = 1$, 25%) and double ventricular extrastimuli ($n = 1$, 25%) from RV apex and/or RV outflow tract. Further, VFs were induced by triple ventricular extrastimuli ($n = 2$, 50%) from the RV apex ($n = 1$, 25%), RV outflow tract ($n = 2$, 50%), and both pacing sites ($n = 1$, 25%). Note that the inducibility of VF was significantly ($p = 0.04$) different among the subgroups in the Brugada group, but not the non-Brugada group. The inducibility of VF (94%, 16/17) in comprised symptomatic patients (symptomatic and syncope group) of the Brugada group was significantly ($p = 0.008$) higher than that (61%, 17/28) in the asymptomatic group of those with Brugada syndrome.

A univariate test was conducted on the clinical examinations for induction of VF and those results are shown in Table 3. Type 1 ECG after pilsicainide test, the maxΔST elevation (≧200 μV), type 1 ECG in control, and positive in late potential had relatively high odds ratios and significance values. However, the multivariate analysis using the linear regression model evaluated the association between baseline clinical factors and the induction of VF. The results are displayed in Table 4, including the odds ratios and 95% confidence intervals. Symptoms indicated the highest odds ratio (odds ratio 31.6; 95% confidence interval: 2.3–430.6; $p = 0.01$) followed by type 1 ECG after pilsicainide test (odds ratio 21.3; 95% confidence interval: 1.67–272.3; $p = 0.02$). Syncope (odds ratio 13.5; 95% confidence interval: 1.2–158.8; $p = 0.04$) also was a significant variable associated with induced VF. However, a family history of sudden cardiac death, type I ECG in the control, positive of late potential, and maxΔST elevation (≧200 μV) did not show significant association with induction of VF.

Follow-up study

ICDs were implanted in 18 patients in the Brugada group (9 symptomatic group, 6 syncope group, 3 asymptomatic group) and in 4 in the non-Brugada group (1 symptomatic, 3 syncope, 0 asymptomatic group). Appropriate shock was delivered in only one patient of the symptomatic group in the Brugada group during the average observation period of 43 ± 14 months. No appropriate shock was delivered to the rest of the patients.

Discussion

Subjects

The subjects in the current study underwent EPS for the diagnosis of Brugada syndrome or risk stratification for patients who had a family history of Brugada syndrome and for the further examination of Brugada-like ECG and/or palpitation and/or syncope. The standard right precordial leads (V1–V3) and an additional six right precordial leads that were located one or two intercostal spaces above the standard right precordial leads (V1–V3) were used for the diagnosis of Brugada type ECG because some patients showed type 1 ECG in additional leads even when normal ECGs were seen in the standard right precordial leads

Table 4 Multivariate analysis for the induction of ventricular fibrillation in the control study.

Variables	*n*	Multivariate analysis		
		OR	95% Confidence intervals	*p*
Symptoms	15	31.6	2.3–430.6	0.01
Syncope	22	13.5	1.2–158.8	0.04
Family history	13	0.4	0.06–2.8	0.37
Type 1 ECG in control	20	1.3	0.3–6.7	0.76
Positive in late potential	37	1.9	0.5–7.4	0.36
Type 1 ECG after pilsicainide test	45	21.3	1.7–272.3	0.02
MaxΔST elevation ($\geqq$200 μV)	38	5.9	0.7–39.3	0.11

Symptoms: documented VF and/or aborted sudden cardiac death; syncope: syncope from unknown etiology; OR, odds ratio; ECG, electrocardiogram.

(V1–V3) [6]. A Na^+ channel-blocker challenge test using pilsicainide can unmask intermittent or concealed Brugada type ECG. However, there is still controversy regarding whether these drugs are specific for Brugada syndrome. Thus, in our study, only type 1 ECG was regarded as Brugada type ECG after the Na^+ channel-blocker challenge test to avoid an overestimate of Brugada syndrome.

Our study showed Brugada syndrome was more common in males (male:female = 12:1), however, there was no significant difference between the Brugada group and non-Brugada group.

Family history may be one of the major risk factors for sudden cardiac death in patients with Brugada syndrome. In our study, in 22% of the Brugada group had a family history while 9% of the non-Brugada group did as well. However, there was no significant difference in the prevalence of family history among the subgroups of the Brugada group. This may suggest that family history has a relatively weaker relationship with the risk of fatal cardiac events than expected, which is consistent with the findings of a meta-analysis of prognostic studies of patients with Brugada syndrome [22]. Gehi et al. [22] suggested that a history of syncope or sudden cardiac death, the presence of a spontaneous type 1 Brugada ECG, and male gender predict a more malignant natural history. They did not recommend the use of a family history of sudden cardiac death, the presence of an SCN5A gene mutation, or EPS to guide the management of patients with a Brugada ECG.

Recently, the Brugada syndrome investigators in Japan [23] reported that the long-term prognosis of probands in non-type 1 group was similar to that of type 1 group and that the presence of early repolarization was also a predictor of poor outcome, which included only probands with Brugada-pattern ST-elevation. Note that the criteria of Brugada syndrome in this study was J point amplitude more than 1 mm in the right precordial leads (V1–V3). Those findings suggested that it was difficult to discriminate high-risk patients only by using a standard 12 ECG. Further examination will be needed to solve this type of issue.

Electrophysiological characteristics in patients of Brugada syndrome

There were no significant differences in the incidence of type 1 ECG and the types 1–3 ECG in the control and those after the pilsicainide test, maxΔST elevation after pilsicainide test and positive in late potential among subgroups of patients with Brugada syndrome (Table 2). There was no significant difference in the ERPs at the RV apex and RV outflow tract at BCL 600 and 400 ms between the Brugada and non-Brugada groups, and among the subgroups of the Brugada group as well as those of the non-Brugada group.

The inducibility of VF was significantly higher in those with Brugada syndrome than the non-Brugada syndrome patients. This may suggest that the inducibility of VF is helpful in identifying individuals at risk of fatal cardiac events, as noted in previous reports [13,24,25]. However, recent large-scale studies [16,17,26] and a meta-analysis [22] on the prognostic studies of patients with Brugada syndrome did not support the usefulness of EPS. A low incidence of arrhythmic events was found in a large Brugada syndrome population [27], with an annual event rate of 2.6% during a follow-up of 3 years. The different results may be caused by the different methods in the stimulation protocol, end-point determination, and/or criteria for positive EPS.

The clinical implication of EPS for the risk stratification in patients with ischemic heart disease and low LV ejection fraction is relatively clear [28], but the usefulness of EPS for the risk stratification in patients with a Brugada ECG remains controversial [14,15]. Though the induction of VF during EPS suggests the existence of electrophysiological substrate of VF, the incidence of spontaneous VF is low in patients with induced VF in asymptomatic Brugada syndrome. One of the reasons is that the spontaneous VF in patients with Brugada syndrome depends mainly on the trigger factors rather than the existence of substrate. However, the existence of VF substrate is also important. Therefore, variables associated with VF induced during EPS in patients without apparent organic heart disease also important. If there is no VF substrate, the spontaneous VF never occurs. It is presumed that negative VF study indicated no risk of VF at that time.

Factors of VF induced by EPS

The univariate analysis indicated the induction of VF in patients without apparent heart disease had a relatively strong relation with type 1 ECG after pilsicainide test, maxΔST elevation ($\geqq$200 μV) and type 1 ECG in control, because those factors had a relatively high incidence in patients with induction of VF. However, the patients in

our study had many complex backgrounds that have some effects on induction of VF. Therefore, we should use the multivariate analysis to determine what variables were independently associated with induction of VF during EPS in patients without organic heart disease.

A linear regression model was used to identify any independent predictors of the induction of VF during the stimulation test. In this manner, the independent predictive value of the relative risk to the induction of VF could be assessed. This analysis showed that symptoms (documented VF and/or aborted sudden cardiac death) had the highest odds ratio. This result is not inconsistent with the general consideration that a history of VF and/or aborted sudden cardiac death is the strongest variable to indicate the existence of substrate of VF in patients without apparent heart disease. Syncope also showed relatively higher odds ratio. This result is also not inconsistent with the general consideration.

Note that type 1 ECG after pilsicainide test also showed high odds ratio in a linear regression model, but not type 1 ECG in control. Type 1 ECG after pilsicainide test, itself, indicates the diagnosis of Brugada syndrome in our study, therefore, the diagnosis of Brugada syndrome itself is strong association with induction of VF during EPS in patients without apparent heart disease. Type 1 ECG after pilsicainide test is superior to type 1 ECG in control for the diagnosis of Brugada syndrome, because pilsicainide unmasks the concealed or intermittent Brugada syndrome. Since the odds ratio shows the relative risk, it is certain that type 1 ECG is important for the diagnosis of Brugada syndrome.

A family history of sudden cardiac death, type 1 ECG in control, positive of late potential, and maxΔST elevation ($\geqq$200 μV) and more did not have significant association with the induction of VF.

These findings suggested that symptoms, syncope, and type 1 ECG after pilsicainide test were independently associated with the electrophysiological substrate of VF in patients without apparent heart disease.

Study limitations

There were several limitations to our study. First, the sample sizes in each group were relatively small, because the subjects were divided into nine groups on the basis of Brugada type ECG and symptoms related to lethal ventricular events and/or brain ischemia. Second, long observation after EPS was not analyzed, because of infrequency of cardiac events. Third, a comprehensive genetic screening was not performed on all patients. Although this may have been ideal, genetic testing is of uncertain yield and is costly.

Conclusions

The electrophysiological characteristics of induced VF in patients without any apparent organic heart disease were assessed. The electrophysiological characteristics in patients with Brugada type ECG were a high inducibility of VF, relatively lower inducibility of VF in patients with asymptomatic patients, and no relationship with the family history. The multivariate analysis revealed that symptoms, syncope, and type 1 ECG after pilsicainide test were independently associated with the inducibility of VF.

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EDITORIAL COMMENTARY

Diagnostic value of bipolar precordial leads in Brugada syndrome: More accurate, more simple, or more theoretical?

Wataru Shimizu, MD, PhD

From the Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan.

In 1992, Pedro and Josep Brugada first described eight patients with a history of aborted sudden cardiac death due to ventricular fibrillation (VF) and a characteristic ECG pattern, consisting of right bundle branch block and ST-segment elevation in the right precordial leads (V_1–V_3), as a distinct clinical entity.[1–8] The presence of right bundle branch block thereafter is considered not to be required for the diagnosis of Brugada syndrome, although mild-to-moderate widening of QRS duration often is observed.[4] Two specific types of ST-segment elevation (coved-type and saddleback) are observed in this syndrome, and the pattern and amplitude of ST-segment elevation often are dynamic.[9] Coved-type ST-segment elevation is more frequently recognized just before and after episodes of VF[9,10] and is reported to be related to a higher incidence of VF and sudden cardiac death.[11] The Second Consensus Report published in 2005 emphasized that type 1 ST-segment elevation, which is defined as a coved ST-segment elevation $\geq$ 0.2 mV at the J point with or without a terminal negative T wave, is required to diagnose Brugada syndrome.[5] Type 2 and type 3 ST-segment elevation, which have a saddleback configuration, are not diagnostic for Brugada syndrome.

ECG recordings of leads V_1 and V_2 at higher (third and second) intercostal spaces have been reported to increase the sensitivity of ECG diagnosis in detecting the Brugada phenotype.[5,12,13] We recently suggested that patients with type 1 ST-segment elevation recorded only at higher V_1–V_2 leads showed a similar prognosis for subsequent cardiac events as did recordings from standard V_1–V_2 leads.[14]

An experimental model of the Brugada syndrome using arterially perfused canine right ventricular wedge preparations[15–18] and several clinical studies[19] have suggested the cellular mechanism of Brugada phenotype, ST-segment elevation, and subsequent VF. A transient outward potassium current (I_{to})–mediated phase 1 notch of the action potential (AP) is greater in the epicardium than in the endocardium in many species, including humans.[20] A net outward shift in current active at the end of phase 1 AP (principally I_{to} and L-type calcium current [$I_{Ca\text{-}L}$]) can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall and producing ST-segment elevation in the ECGs recorded from wedge preparations.[15–18] In the setting of coved-type ST-segment elevation, heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium creates marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which precipitate VF.[15–18] The Brugada syndrome seems to be a clinical counterpart of the mechanism of all-or-none repolarization in the epicardial cells and phase 2 reentry-induced premature beats between adjacent epicardial cells. Therefore, higher sensitivity for ECG diagnosis of Brugada syndrome by recordings of higher V_1–V_2 leads is expected to be due to a higher or wider distribution of abnormal epicardial cells in the right ventricular outflow tract area in some patients with Brugada syndrome.

In a study reported in this issue of *Heart Rhythm,* Batchvarov et al[21] hypothesized that a bipolar precordial lead with a positive electrode at V_2 and a negative electrode at V_4 or V_5 (subtracting lead V_4 or V_5 from V_2 [V_{2-4}, V_{2-5}]) could detect with greater sensitivity the diagnostic type 1 Brugada ECG than could the standard unipolar V_2 lead. They retrospectively analyzed a digital ECG database recorded during diagnostic ajmaline testing in 128 patients with suspected Brugada syndrome. During 21 positive ajmaline tests, the type 1 pattern was observed in the higher V_2 lead (third intercostal space [V_{2h}]) during 20 tests (95.2%) and in lead V_2 during 10 tests (47.6%). The type 1 pattern appeared in lead V_{2-4} or V_{2-5} in all tests when it was present in V_2 and in seven tests during which it was observed in lead V_{2h} but not V_2 (total of 17 [81%] tests). In contrast, the type 1 pattern was observed in lead V_{2-4} or V_{2-5} during 2 (1.9%) negative tests and in 1 (0.5%) healthy subject. The authors concluded that bipolar leads V_{2-4} and V_{2-5} were more sensitive than the standard lead V_2 for detection of the type 1 Brugada ECG pattern but were less sensitive than the higher lead V_2. Regarding the mechanism un-

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derlying the type 1 Brugada ECG pattern in the bipolar precordial leads, the authors speculated that leads V_{2-4} and V_{2-5} reflect the voltage difference between epicardial cells in right ventricular outflow tract regions and those in left ventricular anterior regions. This may be true because left ventricular epicardial cells show an intrinsically smaller phase 1 AP notch than do right ventricular epicardial cells. The precordial bipolar leads (V_{2-4} and V_{2-5}) can be derived from standard 12-lead ECGs with the help of a software upgrade. This may be a major advantage of this method because recording of higher V_1–V_2 leads would require an ECG recorder capable of simultaneous acquisition of 14 leads. The clinical significance of the precordial bipolar leads can be meaningfully established in relation to the presence of symptoms or arrhythmic events. It is possible that a much larger number of ECG recordings will be investigated in retrospective fashion to establish the diagnostic value of the precordial bipolar leads (V_{2-4} and V_{2-5}) in patients with Brugada syndrome. A prospective study would be required to confirm the prognostic value of the precordial bipolar leads.

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How the knowledge of genetic "makeup" and cellular data can affect the analysis of repolarization in surface electrocardiogram☆

Wataru Shimizu, MD, PhD*,[1]

Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

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Abstract This review article sought to describe patterns of repolarization on the surface electrocardiogram in inherited cardiac arrhythmias and to discuss how the knowledge of genetic makeup and cellular data can affect the analysis based on the data derived from the experimental studies using arterially perfused canine ventricular wedge preparations. Molecular genetic studies have established a link between a number of inherited cardiac arrhythmia syndromes and mutations in genes encoding cardiac ion channels or membrane components during the past 2 decades. Twelve forms of congenital long QT syndrome have been so far identified, and genotype-phenotype correlations have been investigated especially in the 3 major genotypes—LQT1, LQT2, and LQT3. Abnormal T waves are reported in the LQT1, LQT2, and LQT3, and the differences in the time course of repolarization of the epicardial, midmyocardial, and endocardial cells give rise to voltage gradients responsible for the manifestation of phenotypic appearance of abnormal T waves. Brugada syndrome is characterized by ST-segment elevation in leads V1 to V3 and an episode of ventricular fibrillation, in which 7 genotypes have been reported. An intrinsically prominent transient outward current (I_{to})-mediated action potential notch and a subsequent loss of action potential dome in the epicardium, but not in the endocardium of the right ventricular outflow tract, give rise to a transmural voltage gradient, resulting in ST-segment elevation, and a subsequent phase 2 reentry-induced ventricular fibrillation. In conclusion, transmural electrical heterogeneity of repolarization across the ventricular wall profoundly affects the phenotypic manifestation of repolarization patterns on the surface electrocardiogram in inherited cardiac arrhythmias.

Keywords: Long QT syndrome; Brugada syndrome; Repolarization; Electrocardiogram; Ventricular arrhythmias

Introduction

Molecular genetic studies during the past 2 decades have revealed a link between mutations in genes encoding for cardiac ion channels or other membrane components and several lethal-inherited cardiac arrhythmias including congenital and acquired long QT syndrome (LQTS), Brugada syndrome, progressive cardiac conduction defect (Lenegre disease), catecholaminergic polymorphic ventricular tachycardia (VT), short QT syndrome, familial atrial fibrillation, and familial sick sinus syndrome.[1] Among these inherited arrhythmias, the congenital LQTS is a Rosetta stone for investigating the genotype-phenotype correlations, because 60% to 70% of clinically affected congenital LQTS patients can be genotyped, and multiple genes encoding the different ion channels or membrane adaptors have been identified.[1] In comparison with congenital LQTS, causative mutations have been less identified in other inherited cardiac arrhythmias except for catecholaminergic polymorphic VT, in which mutations in cardiac *RyR2* gene can be found in approximately 60% of affected patients.[1] In Brugada syndrome, the first mutation was identified in an α-subunit of sodium channel gene, *SCN5A*, in 1998.[2] However, recent worldwide cohort has reported that mutations in *SCN5A* gene can be identified in only 11% to 28% of clinically diagnosed Brugada patients even in experienced institutes.[3] Moreover,

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* Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan.

E-mail address: wshimizu@hsp.ncvc.go.jp

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only 7 genotypes have been so far identified, and most of mutations in genes other than *SCN5A* were found in a single family or small number of families. Therefore, the genotype-phenotype correlations have been much less examined in genotyped patients with Brugada syndrome.[1] The purposes of this review article were (1) to describe patterns of repolarization on the surface electrocardiogram (ECG) in inherited cardiac arrhythmias: congenital LQTS and Brugada syndrome, and (2) to discuss how the knowledge of genetic makeup and cellular data can affect the analysis based on the data derived from the experimental studies using arterially perfused canine ventricular wedge preparations.

Congenital LQTS (Romano-Ward syndrome)

Congenital LQTS is characterized by prolongation of ventricular repolarization and trademark polymorphic VT known as torsade de pointes (TdP).[4] Clinical diagnosis of congenital LQTS is on the basis of prolongation of QT interval in the ECG, cardiac events such as syncope, aborted cardiac arrest or sudden cardiac death, and a family history of apparent LQTS.[5]

Genotype

Molecular genetic studies have revealed 12 forms of Romano-Ward–type congenital LQTS caused by mutations in genes of potassium, sodium, and calcium channels or the membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17, 20, and 21.[1] *KCNQ1* and *KCNE1*, α- and β-subunits of the potassium channel gene, are responsible genes for LQT1 and LQT5, and their mutations result in a decrease (loss of function) in the slowly activating component of the delayed rectifier potassium current (I_{Ks}). Similarly, mutations in *KCNH2* and *KCNE2*, α- and β-subunits of the potassium channel gene, cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}), which are responsible for LQT2 and LQT6 forms. On the other hand, mutations in *SCN5A*, the gene encoding α-subunit of the sodium channel, increase (gain of function) the late sodium current (I_{Na}), responsible for LQT3. Mutations in *KCNJ2* encoding the inward rectifier potassium current (I_{K1}) prolong QT interval associated with periodic paralysis and dysmorphic features, underlying Andersen syndrome (LQT7). A mutation in *Ankyrin-B*, a member of a family of versatile membrane adapters, produces intracellular calcium overload, which underlies LQT4 syndrome. *CACNA1C* is a responsible gene in LQT8, and mutation in *CACNA1C* results in increase of the L-type calcium current ($I_{Ca\text{-}L}$), producing dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism, in addition to QT prolongation. *CAV3* encoding caveolin-3 and *SCN4B* encoding $Na_{\gamma}B4$, an auxiliary subunit of the cardiac sodium channel, are linked to LQT9 and LQT10, respectively. Mutations in both genes result in a gain of function of late I_{Na}, causing phenotype like that in LQT3. A mutation in *AKAP-9*, which encodes Yotiao and assembles *KCNQ1*, is responsible for LQT11. Mutations in syntrophin-α1 (*SNTA1*), a cytoskeletal protein that interacts with the cardiac sodium channel, are most recently reported to be responsible for LQT12 with an LQT3-like phenotype. In all 12 genotypes, decreases in outward potassium currents (I_{Ks}, I_{Kr}, I_{K1}) or increases in inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) prolong the action potential (AP) duration (APD), resulting in prolongation of QT interval, a common phenotype in LQTS. The 3 major genotypes, the LQT1, LQT2, and LQT3, constitute more than 90% of genotyped patients with LQTS.[1]

Cellular basis of abnormal surface ECG

In 1995, Moss and coworkers[6] first suggested genotype-specific T-wave morphology in the surface ECG. Broad-based prolonged T waves are the specific T-wave pattern observed in LQT1, whereas low-amplitude T waves with a notched or bifurcated configuration are more frequently observed in LQT2. On the other hand, late-appearing T waves with a prolonged isoelectric ST segment are more specific in LQT3. A series of experimental studies using arterially perfused canine left ventricular (LV) wedge preparations have revealed that intrinsic transmural electrical heterogeneity of ventricular repolarization from the epicardial, midmyocardial (M), and endocardial cells contributed to ST-T morphology and the QT interval on ECG, especially in the left precordial (V4-V6) leads, which are thought to reflect the potentials of the LV anterolateral wall.[7-10] Under normal conditions, repolarization of the epicardial AP occurs first and coincides with the peak of the normal T wave, whereas repolarization of the longest AP in the M layer coincides with the end of the T wave. Repolarization of endocardial cells usually occurs between repolarization of epicardial and M cells. The amplified transmural electrical heterogeneity of ventricular repolarization associated with differential modification of ionic currents in each cell type, which is caused by mutations in each LQTS gene, results in genotype-specific T-wave morphology in the ECG.[7,8,10]

The cellular basis for abnormal T waves in the LQT1, LQT2, and LQT3 syndromes has been demonstrated by pharmacologic LQTS models using arterially perfused LV wedge preparations (Fig. 1).[7,8,10] A specific I_{Ks} blocker, chromanol 293B, and a β-adrenergic agonist, isoproterenol are used to mimic LQT1.[8,10] Although I_{Ks} block alone produces a homogeneous prolongation of repolarization in the 3 cell types, addition of isoproterenol abbreviates the APD in the epicardial and endocardial cells but not in the M cells, resulting in a dramatic augmentation of transmural dispersion of repolarization (TDR) and a broad-based T wave (Fig. 1A, E).[8] An I_{Kr} blocker, D-sotalol in the presence of hypokalemia is used to simulate LQT2.[7,10] I_{Kr} block preferentially prolongs the APD in the M cells than that in the epicardial or endocardial cell and slows phase 3 of the AP in all 3 cell types, producing a large TDR and a low amplitude T wave with a notched or bifurcated appearance (Fig. 1B, G).[7] Augmentation of late I_{Na} with ATX-II, a sea anemone toxin, is used to mimic LQT3.[7,10] ATX-II increases the TDR by greater prolongation of the M cell APD than that of epicardial or endocardial cell APD. Moreover, ATX-II also produces larger effect on the APD in the epicardial and

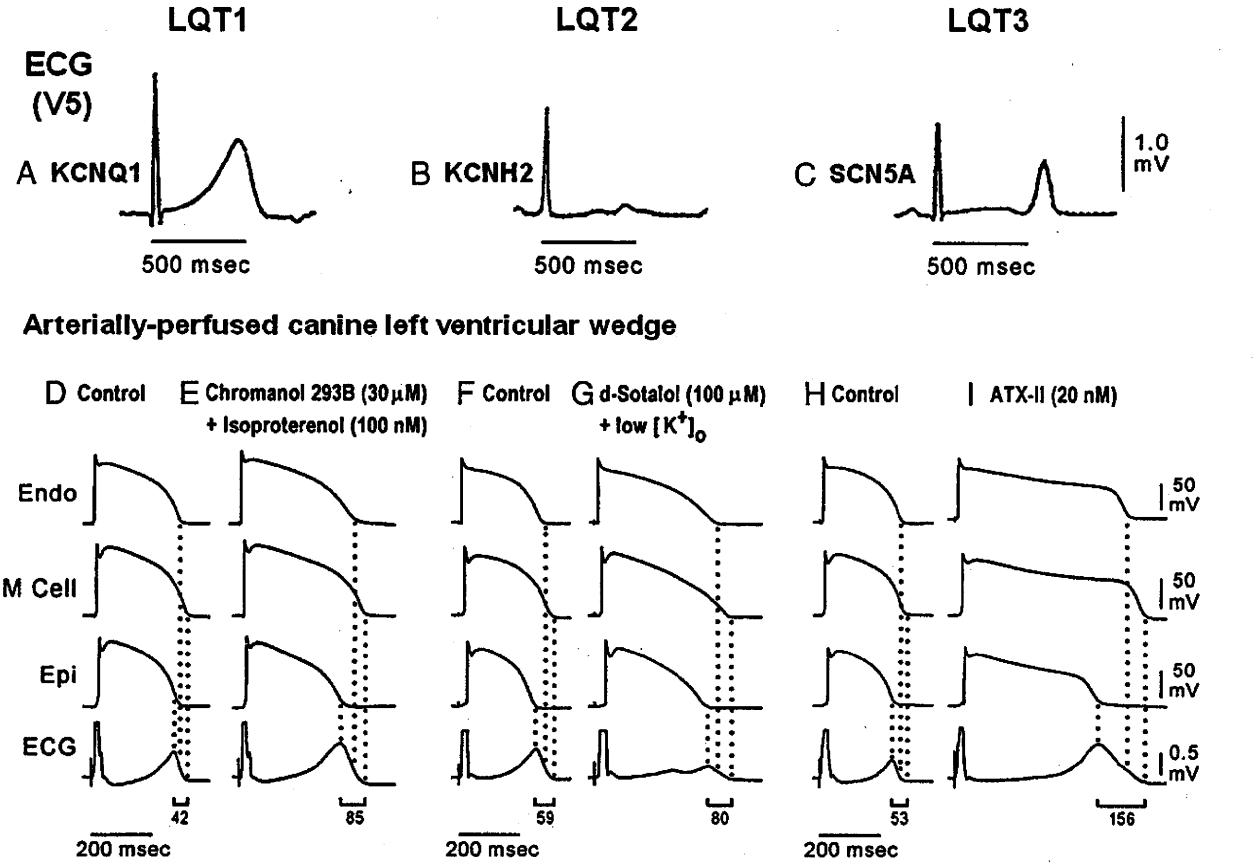

Fig. 1. Cellular basis of abnormal T-wave patterns in LQT1, LQT2, and LQT3 syndrome. A–C, Electrocardiographic lead V5 recorded in patients with LQT1, LQT2, and LQT3 forms of congenital LQTS. D–I, Transmembrane APs recorded simultaneously from endocardial (Endo), midmyocardial (M), and epicardial (Epi) cells together with a transmural ECG at a BCL of 2000 milliseconds in the 3 models of the arterially perfused canine LV wedge preparations. Pharmacologic models mimic the phenotypic appearance of the abnormal T waves in all 3 models. Modified from Shimizu and Antzelevitch[7,8] with permission.

endocardial cells, resulting in a marked delay in the onset of the T wave consistent with the late-appearing T-wave pattern (Fig. 1C, I).[7]

Cellular basis of TdP

In the experimental models of the LQT1, LQT2, and LQT3 syndromes using arterially perfused canine LV wedge preparations, TdP develops spontaneously or can be easily induced by a single extrastimulus applied to the epicardium, where the APD is shortest.[7,8,10] In all 3 models, the first premature beat that initiates TdP displays a relatively narrow positive QRS deflection, similar to that of the basic beats which are stimulated from the endocardial site, indicating that it originates in the deep subendocardium either in the Purkinje cells or M cells. However, subsequent TdP is thought to be due to reentrant mechanism, because a large TDR is required to induce TdP, and TdP is most easily induced by a single extrastimulus introduced at epicardial cell, the site of the shortest APD.

Brugada syndrome

Characteristic of the ECG pattern in Brugada syndrome is a coved-type ST-segment elevation (type 1) in the V1 and V2 leads,[11,12] which is defined as an ST-segment elevation displaying J wave or ST-segment amplitude of 0.2 mV or greater with or without a terminal negative T wave. The lethal ventricular arrhythmia is ventricular fibrillation (VF) in Brugada syndrome.

Genotype

After the first mutation linked to Brugada syndrome was found in *SCN5A* in 1998,[2] a total of 7 causative genes (genotypes) have been reported.[1,13] Mutations in *CACNA1C* or *CACNB2* encoding the α1- or β2b-subunit of the L-type calcium channel were identified in 3 probands with Brugada like ST-segment elevation associated with a short QT interval. Functional studies for the mutations demonstrated loss of function of $I_{Ca\text{-}L}$, thus causing both Brugada and short QT phenotype. Thereafter, a mutation in a conserved amino acid of the glycerol-3-phosphate dehydrogenase 1-like (*GPD1-L*) gene was found in affected individuals of a large Brugada family. The *GPD1-L* mutation decreases *SCN5A* surface membrane expression and reduces I_{Na}, thus causing Brugada syndrome. A nonsense mutation in *SCN1B* encoding a function-modifying sodium channel β1-subunit was then identified in a family with Brugada syndrome associated with cardiac conduction disease. Both phenotypes are attributable to the loss of I_{Na} current when α-subunit ($Na_v1.5$) of the sodium

channel was coexpressed with the mutant β1-subunit. More recently, a missense mutation in *KCNE3*, which encodes a potassium channel β-subunit and interacts with Kv4.3 (transient outward current: I_{to}) channel, was identified in a proband with Brugada syndrome. Brugada phenotype is responsible to the gain of function of I_{to} intensity by coexpression of the mutant *KCNE3* with *KCND3*, which encodes Kv4.3. Most recently, a mutation in *SCN3B* encoding a sodium channel β3-subunit was identified in a patient with Brugada syndrome.[13] Coexpression of the mutant *SCN3B* with wild-type *SCN5A* and wild-type *SCN1B* leads to loss of function of I_{Na} current, thus responsible for Brugada phenotype. In all 7 genotypes, decreases in inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) or increases in outward potassium currents (I_{to}) produce Brugada phenotype. However, approximately two thirds of Brugada patients have not yet been genotyped, suggesting the presence of genetic heterogeneity.[1]

Cellular basis of type 1 ECG

An experimental model of Brugada syndrome using arterially perfused canine right ventricular (RV) wedge preparations unmasked the cellular mechanism of Brugada phenotype, ST-segment elevation, and subsequent VF.[14] The I_{to}-mediated AP notch and the loss of the AP dome in the epicardial cells, but not in the endocardial cells, of the right ventricle give rise to a transmural voltage gradient, producing ST-segment elevation in the ECG in the wedge preparations. Fig. 2 illustrate superimposed transmembrane APs simultaneously recorded from epicardial and endocardial sites, together with a transmural ECG. Under control conditions (Fig. 2A), a small J wave coincides with the small notch observed in epicardial cell, but not in endocardial cell.

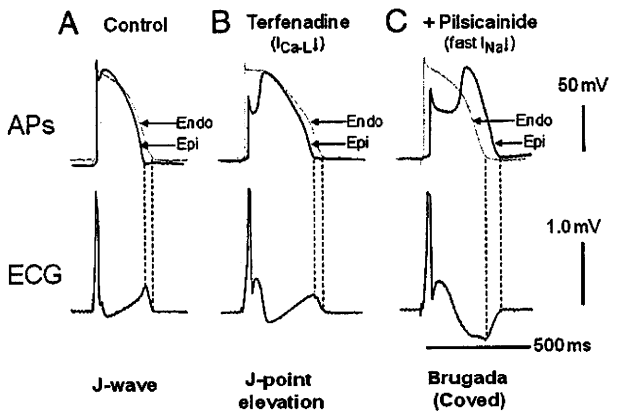

Fig. 2. The cellular basis for ST-segment elevation in a Brugada model using an arterially perfused canine RV wedge preparation. Shown are superimposed transmembrane APs simultaneously recorded from epicardial (Epi) and endocardial (Endo) sites together with a transmural ECG (BCL = 2000 milliseconds). A, Control. B, $I_{Ca\text{-}L}$ block with terfenadine (5 μmol/L) accentuates the phase 1 notch in Epi but not in Endo and causes J-point elevation. C, Additional pilsicainide (5 μmol/L), mimicking *SCN5A* (sodium channel) defect, produces further accentuation of the phase 1 notch, a greater prolongation of Epi AP, and a reversed transmural voltage gradient, giving rise to coved type ST-segment elevation with a terminal negative T wave.

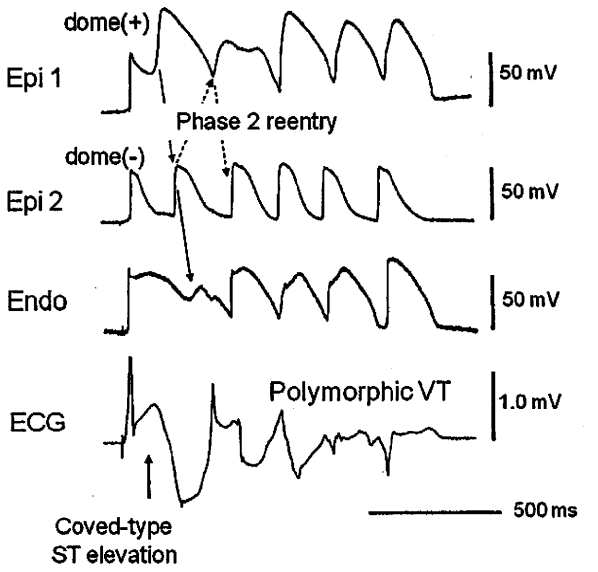

Fig. 3. Coved-type ST-segment elevation and subsequent nonsustained polymorphic VT caused by premature beats induced by phase 2 reentry in a Brugada model, using an arterially perfused canine RV wedge preparation. Transmembrane AP simultaneously recorded from 2 epicardial (Epi 1 and 2) sites and 1 endocardial (Endo) site together with a transmural ECG (BCL 2000 milliseconds). In the setting of heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium and a remarkable coved type ST-segment elevation in the ECG with a combined administration with terfenadine and pilsicainide, electrotonic propagation from the site where the dome is restored (Epi 1) to the site where it is lost (Epi 2) results in development of a premature beat induced by phase 2 reentry, triggering a spontaneous polymorphic VT. Modified from Shimizu et al[15] with permission.

An $I_{Ca\text{-}L}$ block with terfenadine amplifies the transmural voltage gradient due to its accentuation of the phase 1 notch in epicardial cell, but not in endocardial cell, resulting in J-point elevation in the ECG (Fig. 2B). A typical type 1 coved ST-segment elevation associated with a terminal negative T wave is created by an additional I_{Na} block with pilsicainide, which produces further accentuated phase 1 AP notch, greater prolongation of epicardial APD, and a resultant reversed transmural voltage gradient (Fig. 2C).

Fig. 3 illustrates nonsustained polymorphic VT via phase 2 reentry induced in a Brugada model using the RV wedge preparation.[15,16] In the setting of remarkable coved type ST-segment elevation with a combined administration with terfenadine and pilsicainide, heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium creates a marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which precipitates nonsustained polymorphic VT. Data of our high-resolution optical mapping system allowing to record transmembrane APs simultaneously from 256 sites suggest that a steep repolarization gradient between a loss of dome region and a restored dome region in the epicardium is essential to produce phase 2 reentry-induced premature beats.[15,16] Phase 2 reentry-induced premature beats have been shown to induce a reentrant pathway rotated in the epicardium and finally involving the transmural myocardium, precipitating nonsustained polymorphic VT or VF.

Conclusions

The data derived from the experimental studies using arterially perfused canine ventricular wedge preparations suggested that transmural electrical heterogeneity of repolarization across the ventricular wall profoundly affects the phenotypic manifestation of repolarization patterns on the surface ECG in inherited cardiac arrhythmias, such as congenital LQTS and Brugada syndrome.

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Neurally Mediated Syncope as a Cause of Syncope in Patients With Brugada Electrocardiogram

MIKI YOKOKAWA, M.D., HIDEO OKAMURA, M.D., TAKASHI NODA, M.D., PH.D., KAZUHIRO SATOMI, M.D., PH.D., KAZUHIRO SUYAMA, M.D., PH.D., TAKASHI KURITA, M.D., PH.D., NAOHIKO AIHARA, M.D., SHIRO KAMAKURA, M.D., PH.D., and WATARU SHIMIZU, M.D., PH.D.

From the Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan

Neurally Mediated Syncope in Brugada Syndrome. ***Introduction:*** **Patients with type 1 Brugada electrocardiogram (ECG) and an episode of syncope are diagnosed as symptomatic Brugada syndrome; however, all episodes of syncope may not be due to ventricular tachyarrhythmia.**

Methods and Results: **Forty-six patients with type 1 Brugada ECG (all males, 51 ± 13 years, 29 spontaneous, 17 Ic-drug induced), 20 healthy control subjects (all males, 35 ± 11 years), and 15 patients with suspected neurally mediated syncope (NMS; 9 males, 54 ± 22 years) underwent the head-up tilt (HUT) test. During the HUT test, 12-lead ECGs were recorded in all patients, and the heart rate variability was investigated in some patients. Sixteen (35%) of 46 patients with Brugada ECG, 2 (10%) of 20 control subjects, and 10 (67%) of 15 patients with suspected NMS showed positive responses to the HUT test. Although no significant differences were observed in HUT-positive rate among Brugada patients with documented VT (7/14; 50%), syncope (5/19; 26%) and asymptomatic patients (4/13; 31%), the HUT-positive rate was significantly higher in patients with documented VT (50%) and those with VT or no symptoms (11/27, 41%) compared to that in control subjects (10%) ($P < 0.05$). Augmentation of ST-segment amplitude (≥0.05 mV) in leads V1-V3 was observed in 11 (69%) of 16 HUT-positive patients with Brugada ECG during vasovagal responses, and was associated with augmentation of parasympathetic tone following sympathetic withdrawal.**

Conclusion: **Thirty-five percent of patients with Brugada ECG showed vasovagal responses during the HUT test, suggesting that some Brugada patients have impaired balance of autonomic nervous system, which may relate to their syncopal episodes.** *(J Cardiovasc Electrophysiol, Vol. 21, pp. 186-192, February 2010)*

autonomic nervous system, Brugada syndrome, head-up tilt test, syncope, sudden death

Introduction

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads V1 through V3 and an episode of ventricular tachyarrhythmia (VT) in the absence of structural heart disease.[1-3] In patients with Brugada syndrome, syncopal episodes are generally thought to be due to VT; however, all episodes of syncope may not be owing to VT events. Neurally mediated syncope (NMS) is 1 of the causes of syncope in general population, and it refers to a reflex response that some triggering factors give rise to arterial vasodilatation associated with relative or absolute bradycardia.[4] In general, the overall prognosis in patients with NMS is quite favorable.[4] On the other hand, the precise cause of syncope in patients with Brugada syndrome is difficult to determine. Therefore, the therapeutic strategy for Brugada patients with syncope is often problematic. The aim of this study was to evaluate the possibility of NMS as a cause of syncope in patients with Brugada electrocardiogram (ECG).

Methods

Patients Population

The study population consisted of 46 consecutive patients with type 1 Brugada ECG who were admitted to the National Cardiovascular Center, Suita, Japan, between May 2004 and March 2006 (all males, ages 26 to 77; mean 51 ± 13 years, 29 spontaneous, 17 Ic-drug induced), 20 healthy control subjects (all males, 35 ± 11 years), and 15 patients suspected of NMS (9 males, 54 ± 22 years). Ethical approval was obtained from the Institutional Review Committee of our hospital, and all patients and control subjects gave their informed, written consent before participation. The control subjects and the patients with suspected NMS showed no structural heart diseases, normal physical examination results, and normal 12-lead ECGs, and received no drug treatment affecting the sympathetic nervous system. Type 1 Brugada ECG was defined as a coved type ST-segment elevation of ≥ 0.2 mV at

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No conflicts of interest were declared.

Address for correspondence: Wataru Shimizu, M.D., Ph.D., Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, 565-8565, Japan. Fax: 81-6-6872-7486; E-mail: wshimizu@hsp.ncvc.go.jp

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J point observed in more than 1 of the right precordial leads (V1 to V3) in the presence or absence of a sodium channel blocker.[2]

Head-Up Tilt Test

The HUT test was performed in the afternoon after 4 hours of fasting in a quiet and comfortable room equipped for cardiopulmonary resuscitation. All patients were allowed to lie on an electrically controlled tilt table an intravenous line containing 5% dextrose was inserted into 1 arm, and allowed to rest in supine position for at least 10 minutes. A positive HUT test was defined by the development of syncope or presyncope associated with relative bradycardia (≥20% decrease in heart rate compared with baseline) or hypotension (systolic blood pressure <80 mmHg). Presyncope was defined as the induction of symptoms of imminent syncope, and syncope was defined as sudden transient loss of consciousness. Positive response to the HUT test was classified into 3 types owing to hemodynamic status, such as vasodepressor type (hypotension without significant bradycardia), cardioinhibitory type (bradycardia without associated hypotention), and mixed type (hypotension followed by bradycardia).[4] At first, we performed passive tilt (Control-Tilt) at an angle of 70 degrees for 30 minutes. When Control-Tilt was negative, sublingual nitroglycerin (NTG) spray 0.3 mg was administered, and the test was continued for 15 minutes (NTG-Tilt). The endpoint of each tilt test was the time when patients showed positive responses or the completion of HUT-protocol.

Parameters Measured During the Head-Up Tilt Test

Heart rate and blood pressure

Heart rate was monitored, and cuff blood pressure was measured by electrosphygmomanometry with a microphone placed over the brachial artery to detect Korotkoff sounds every minute (STBP-780, Colin Electronics, Komaki, Japan) in all patients during the HUT test.

ST-segment amplitude in the right precordial leads

Twelve-lead ECGs were recorded every 1 minute during the HUT test, and the changes of ST-segment amplitude in the right precordial leads (V1-V3) were analyzed (ML-6500, Fukuda-denshi, Tokyo, Japan) in all patients during the HUT test.

Heart rate variability

Six-lead ECGs from the Task Force Monitor (CNSystem, Graz, Austria)[5-7] were measured for beat-to-beat heart rate and consecutive R-R intervals in 10 patients with Brugada ECG (4 documented VT, 5 syncopal episode only, and 1 asymptomatic), 9 control subjects, and 5 patients with suspected NMS. The heart rate variability (HRV) was investigated by a power spectral analysis delineating the low-frequency component (LF; 0.04–0.15 Hz) and the high-frequency component (HF; 0.15–0.40 Hz).[8] We analyzed the normalized unit of the HF components (%) calculated automatically (HF/power spectral density-very low-frequency component [0–0.04 Hz] × 100)[8,9] and the LF/HF ratio. The HF indicates the tone of the parasympathetic nervous system, and the LF/HF ratio indicates the sympathovagal balance.

Statistical Analysis

Numerical values were expressed as means ± SD unless otherwise indicated. Comparisons of parameters between 2 groups were made using the unpaired Student *t*-test. Comparisons of parameters among 3 groups were made with a one-way analysis of variance (ANOVA), followed by the Scheffe's multiple-comparison test. Categorical variables were compared using a chi-square analysis using the Yate's correction or Fisher exact test if necessary. An overall chi-square test for a 2 × n table was performed when comparisons involved >2 groups. A P-value < 0.05 was considered significant.

Results

Clinical Characteristics

The clinical characteristics of 46 patients with Brugada ECG and 15 patients with suspected NMS are shown in Table 1. The patients with Brugada ECG were divided into 3 groups: (1) 14 patients with documented VT; (2) 19 patients with syncopal episodes only; and (3) 13 asymptomatic patients. No significant differences were observed in age, incidence of spontaneous type 1 ECG, family history of sudden cardiac death (SCD), induced ventricular fibrillation during electrophysiologic study (EPS), and *SCN5A* mutation. Implantable cardioverter-defibrillator (ICD) was implanted more frequently in patients with documented VT. The triggers of VT and/or syncope are also shown in Table 1. Seventy-nine percent of VT episodes occurred during sleep or at rest in patients with documented VT ($P < 0.0001$ vs the patients with syncopal episodes only and suspected NMS). On the other hand, in patients with syncopal episodes only, 15% of syncopal episodes occurred after urination, 21% during standing, and 21% after drinking alcohol, which seemed to be similar patterns in patients with suspected NMS. Based on the clinical description of the syncopal events, 16 (84%) of 19 Brugada patients with syncopal episodes were suspected to have NMS. Syncopal episodes seemed to be due to VT in 1 of the remaining 3 patients.

Positive Response to the Head-Up Tilt Test

Comparison of the positive responses to the HUT test between 46 patients with Brugada ECG and 20 control subjects along with 15 patients with suspected NMS are shown in Table 2. Sixteen (35%) of 46 patients with Brugada ECG showed positive responses. Positive responses were developed in 1 (2%) of 46 patients during Control-Tilt and in 15 (33%) of 45 patients during NTG-Tilt, and the mixed type was predominant (94%). In patients with Brugada ECG, there were no significant differences in the incidence of positive responses among patients with documented VT (50%), those with syncopal episodes only (26%), and asymptomatic patients (31%). No significant differences were observed in the type of positive responses between the 3 groups. The mixed type was predominant (100%, 100%, and 75%, respectively), and cardioinhibitory type was not observed in all 3 groups. Two (10%) of 20 control subjects and 10 (67%) of 15 patients with suspected NMS showed positive responses. The HUT-positive rate was not significantly different between all 46 patients with Brugada ECG, 20 control subjects and 15 subjects with suspected NMS (35% vs 10% vs 67%);

TABLE 1
Clinical Characteristics of Patients with Brugada Electrocardiogram and Suspected NMS

	Documented VT (n = 14)	Syncopal Episodes only (n = 19)	Asymptomatic (n = 13)	Suspected NMS (n = 15)
Age (years)	50 ± 15	51 ± 12	52 ± 14	54 ± 22
Spontaneous type 1 ECG	10 (71)	9 (47)	10 (77)	–
Family history of SCD	4 (29)	4 (21)	4 (31)	–
Induced VF during EPS	10/12 (83)	15/18 (83)	8/11 (73)	–
SCN5A mutation	1 (7)	3 (16)	0 (0)	–
ICD implantation	14 (100)	13 (68)*	7 (54)*	–
Triggers of syncope				
During sleeping or at rest	11 (79)	1 (5)*	–	0*
After urination	0	3 (15)	–	1 (7)
Prolonged standing at attention	0	4 (21)	–	4 (27)
After drinking alcohol	0	4 (21)	–	6 (40)
After meal	1 (7)	0	–	0
After exertion	0	2 (11)	–	2 (13)
After sudden unexpected pain	0	2 (11)	–	0
During driving	0	1 (5)	–	0
Others	2 (14)	2 (11)	–	2 (13)

Values are mean ± SD for age, and expressed as frequency (%). *P < 0.05 vs documented VT group. ECG = electrocardiogram; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; NMS = neurally mediated syncope; SCD = sudden cardiac death; VT = ventricular tachyarrhythmias; VF = ventricular fibrillation.

however, the HUT-positive rate was significantly higher in 14 patients with documented VT (50%) and 27 patients with VT or no symptoms (41%) compared to that in control subjects (10%) (P = 0.03, P = 0.04, respectively). The HUT-positive rate in 19 Brugada patients with syncopal episodes (26%) was significantly lower than that in 15 patients with suspected NMS (P = 0.04), although the syncopal episodes in 84% of the 19 patients were suspected to be due to NMS. Positive responses to the HUT test were more frequency observed in 15 patients with suspected NMS compared to those in 20 control subjects (10/15 vs 2/20; P < 0.001).

Comparison of the clinical characteristics between 16 HUT-positive patients and 30 HUT-negative patients with Brugada ECG were shown in Table 3. No significant differences were observed in cardiac events, such as documented VT or syncope. Furthermore, there were no significant differences in the clinical characteristics, such as age, spontaneous type 1 ECG, a family history of SCD, inducibility of ventricular fibrillation during EPS, *SCN5A* mutation, and ICD implantation.

Response of Heart Rate and ST-Segment Amplitude

In patients with Brugada ECG, the heart rate was increased by 12 ± 9 beats/min during Control-Tilt, and by 24 ± 14 beats/min during NTG-Tilt. As the heart rate was increased, decrease of ST-segment amplitude of ≥ 0.05 mV from baseline in the right precordial leads was observed in 11 (24%) of 46 patients during Control-Tilt (−0.14 ± 0.08 mV), and in 19 of 45 (42%) patients during NTG-Tilt (−0.15 ± 0.10 mV) (Fig. 1C). However, augmentation of ST-segment amplitude of ≥ 0.05 mV in the right precordial leads was observed just before and after positive responses to the HUT test in 11 (69%) of 16 HUT-positive patients (0.10 ± 0.06 mV) (Figs. 1D and E). These significant ST-segment augmentation was observed in 1 patient during Control-Tilt (documented VT), and 10 patients during NTG-Tilt (5 documented VT, 2 syncopal episodes only, 3 asymptomatic), respectively. On the other hand, augmentation of the ST-segment amplitude of ≥ 0.05 mV was 2 (7%) of 30 HUT-negative patients during NTG-Tilt (1 documented VT, 1 syncopal episodes only). As a result, the average ST-segment augmentation was

TABLE 2
Responses to Head-Up Tilt Test in Patients with Brugada Electrocardiogram, Control Subjects, and Patients with Suspected NMS

	All (n = 46)	Documented VT (n = 14)	Syncopal Episodes Only (n = 19)	Asymptomatic (n = 13)	Brugada ECG with VT or No Symptoms (n = 27)	Control Subjects (n = 20)	Suspected NMS (n = 15)
Age (years)	51 ± 13*	50 ± 15*	51 ± 12*	52 ± 14*	51 ± 14*	35 ± 11	54 ± 22*
Positive response	16 (35)	7 (50)*	5 (26)†	4 (31)	11 (41)*	2 (10)	10 (67)*
Control-tilt	1/46 (2)	1/14 (7)	0/19 (0)	0/13 (0)	1/27 (4)	0/20 (0)	0/15 (0)
NTG-tilt	15/45 (33)†	6/13 (46)*	5/19 (26)†	4/13 (31)	10/26 (38)	2/20 (10)	10/15 (67)*
Type of positive response							
Vasodepressive	1/16 (6)	0	0	1/4 (25)	1/11 (9)	0	1/10 (10)
Cardioinhibitory	0	0	0	0	0	0	0
Mixed	15/16 (94)	7/7 (100)	5/5 (100)	3/4 (75)	10/11 (91)	3 (100)	9/10 (90)

Values are expressed as frequency (%). *P < 0.05 vs control subjects, †P < 0.05 vs suspected NMS. ECG = electrocardiogram; NMS = neurally mediated syncope; NTG = nitroglycerin; VT = ventricular tachyarrhythmias.

TABLE 3

Comparison of Clinical Characteristics Between Head-up Tilt-Positive Patients and Head-up Tilt-Negative Patients

	HUT-Positive (n = 16)	HUT-Negative (n = 30)	P-value
Age (years)	52 ± 13	50 ± 14	0.58
Documented VT	7 (44)	7 (23)	0.15
Syncope only	5 (31)	14 (47)	0.49
Asymptomatic	4 (25)	9 (30)	0.99
Spontaneous type 1 ECG	11 (69)	18 (60)	0.79
Family history of SCD	4 (25)	8 (27)	1.0
Induced VF during EPS	13/15 (87)	20/26 (77)	0.72
SCN5A mutation	1 (6)	3 (10)	1.0
ICD implantation	14 (88)	24 (80)	0.82

Values are expressed as frequency (%). ECG = electrocardiogram; EPS = electrophysiological study; HUT = head-up tilt test; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; VT = ventricular tachyarrhythmias; VF = ventricular fibrillation.

significantly larger in 16 HUT-positive patients than in 30 HUT-negative patients at similar heart rate (0.06 ± 0.06 mV vs −0.04 ± 0.06 mV, $P < 0.0001$). No ventricular arrhythmias were induced during the HUT test in any patients with Brugada ECG. The ST-segment augmentation was not observed during the HUT test in any control subjects (−0.02 ± 0.02 mV, $P < 0.0001$ vs 16 HUT-positive Brugada patients) and patients with suspected NMS (−0.02 ± 0.04 mV, $P < 0.001$ vs 16 HUT-positive Brugada patients; Fig. 2).

Heart Rate Variability and ST-segment Amplitude

Positive responses during NTG-Tilt were observed in 4 (40%) of 10 patients with Brugada ECG, in 1 (11%) of 9 control subjects, and in 4 (80%) of 5 patients with suspected NMS in whom the HRV was monitored. The autonomic activities in a representative NTG-Tilt-positive patient with Brugada ECG and those with suspected NMS are shown in Figure 3A and B, respectively. Before positive responses to the HUT test, sympathetic activity (LF/HF ratio) dramatically increased; and then, sympathetic withdrawal occurred immediately. Thereafter, parasympathetic nerve activity (the normalized unit of the HF components) gradually increased. The similar pattern of augmented parasympathetic nerve activity following sympathetic withdrawal during positive responses to the HUT test was observed in all 9 HUT-positive patients. The patterns of HRV were not different among the HUT-positive patients with Brugada ECG, the HUT-positive control subjects, and the HUT-positive patients with suspected NMS. In 3 (75%) of 4 HUT-positive patients with Brugada ECG, the LF/HF ratio decreased and the HF component increased gradually toward the maximum ST-segment elevation just before and after positive response for the HUT test (Fig. 3A), but ST-segment was decreased in patients with NMS (Fig. 3B).

Discussion

In this study, 35% of patients with Brugada ECG showed vasovagal responses during the HUT test regardless of the presence VT or syncope. The HUT test was also positive in 41% among only Brugada patients with documented VT or no symptoms. During vasovagal response, ST-segment augmentation in the right precordial leads (V1-V3) was observed in 11 (69%) of 16 HUT-positive patients with Brugada ECG, but no ventricular arrhythmias were induced in any HUT-positive patients.

Neurally Mediated Syncope as a Cause of Syncope in Brugada Syndrome

Several case reports have described patients exhibiting clinical phenotype of both Brugada syndrome and NMS.[10-12]

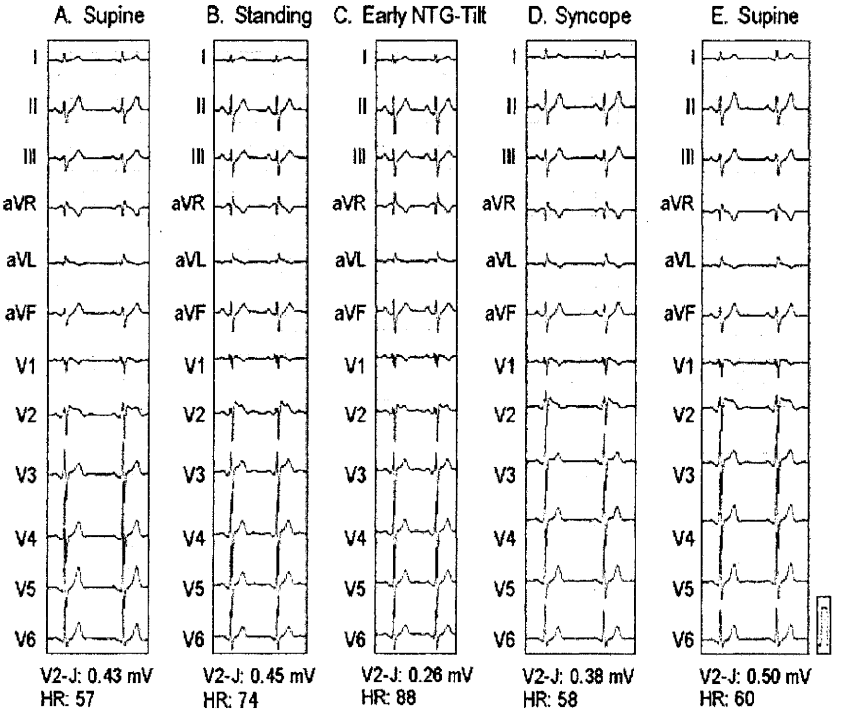

Figure 1. *The12-leads electrocardiogram (ECG) during head-up tilt test in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada ECG at supine position (A), at standing position (B), at early phase of NTG-Tilt (C), at syncope (D), and at supine position following syncope (E). The ST-segment elevation was decreased from 0.45 mV to 0.26 mV at early phase of NTG-Tilt as the heart rate was increased (C), while it was augmented to 0.38 mV at syncope (D), and to 0.50 mV at supine position following syncope (E).*

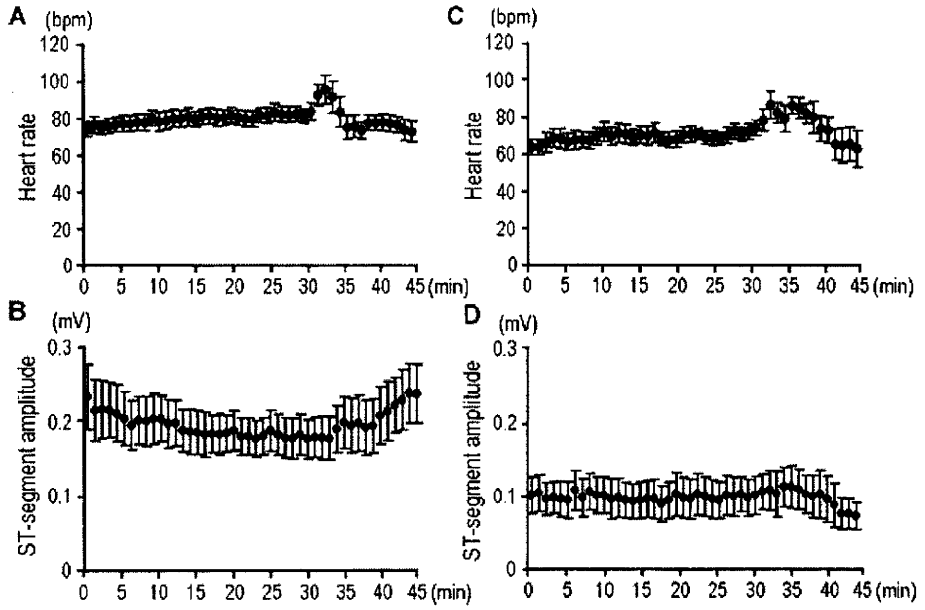

Figure 2. *Response of the heart rate and ST-segment amplitude during the head-up tilt (HUT) test in 16 HUT-positive patients with Brugada electrocardiogram (ECG) (A, B) and in 10 HUT-positive patients with suspected neurally mediated syncope (NMS) (C, D). At first, the passive tilt (Control-Tilt) was performed for 30 minutes (0–30 minutes). When Control-Tilt was negative, nitroglycerin tilt was continued for 15 minutes (30–45 minutes). The responses of heart rate during positive responses to the HUT test were similar in patients with Brugada ECG (A) to those in patients with suspected NMS (C). In patients with Brugada ECG, ST-segment in lead V2 was augmented before and after positive responses to the HUT test (B), but not in those with suspected NMS (D).*

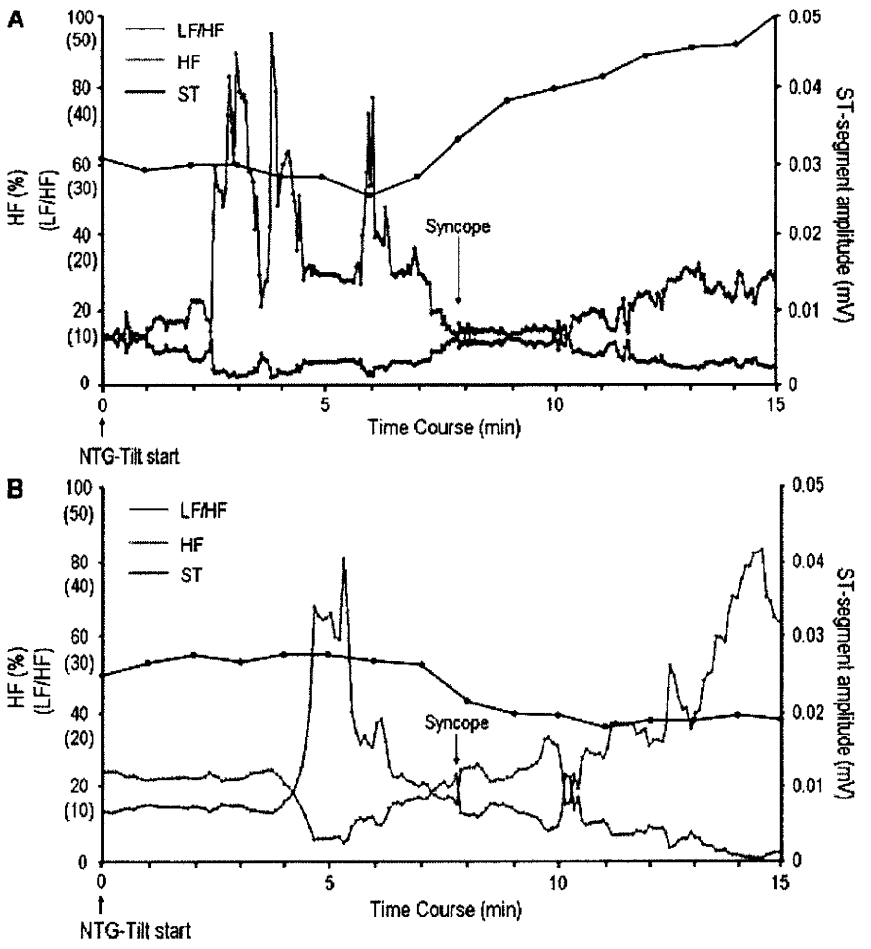

Figure 3. *Autonomic responses during head-up tilt (HUT) test. The autonomic activities in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada electrocardiogram (ECG) (A) and those in a representative NTG-Tilt-positive patient with suspected NMS (B). Before tilt-induced syncope, sympathetic activity (LF/HF ratio) dramatically increased; and then, sympathetic withdrawal occurred immediately. Thereafter, parasympathetic nerve activity (the normalized unit of the HF components) gradually increased. In the HUT-positive patient with Brugada ECG, ST-segment augmentation in lead V2 was observed just before and after positive responses, and the LF/HF ratio decreased and the HF component increased gradually toward the maximum ST-segment elevation (A). In contrast, in the HUT-positive patient with suspected NMS, ST-segment amplitude in lead V2 was decreased gradually after positive responses (B).*

It is well known that the autonomic nervous system plays an important role on the arrhythmogenesis of Brugada syndrome. Previous studies showed that the withdrawal of sympathetic activity and the sudden rise in vagal activity was an important triggering factor of ventricular fibrillation.[13-15] Similarly, it has been presumed that parasympathetic tone increase during NMS events in patients with Brugada ECG. Recent basic study showed that *SCN5A*, a major responsible gene in Brugada patients, is expressed not only in the myocardial cells but also in intracardiac ganglia.[16] Makita *et al.* also demonstrated a novel nonsense mutation in *SCN5A* gene in a patient with Brugada syndrome who had been diagnosed as NMS.[17] These results suggested that the abnormal regulation or imbalance of autonomic nervous system may exist regardless of the presence or absence of cardiac events in patients with Brugada ECG.

ST-Segment Elevation in the Precordial Leads During the HUT Test in Patients with Brugada ECG

In Brugada syndrome, spontaneous augmentation of ST-segment elevation occurred along with an increase in vagal activity, especially just before and after the occurrence of ventricular fibrillation.[14] The ST-segment elevation is also known to be modulated by exercise,[18] pharmacological interventions that interact with automatic nervous activities,[19] or taking meals associated with glucose-induced insulin levels.[20] In this study, ST-segment augmentation in the right precordial leads was observed just before and after positive responses to the HUT test in two-thirds (69%) of the HUT-positive patients with Brugada ECG but only in 7% of the HUT-negative patients. In patients with Brugada ECG, the preceding increase of sympathetic nerve activity during the HUT test may cause augmentation of ICa-L, resulting in attenuation of ST-segment elevation.[19] Subsequent augmentation of parasympathetic nerve activity during the HUT test may decrease of ICa-L, and increase Ito, thus augmenting ST-segment amplitude.

Clinical Implication

The second consensus report suggested that symptomatic patients displaying type 1 Brugada ECG (either spontaneous or after class Ic drugs) who present with aborted sudden death should undergo ICD implantation.[3] ICD implantation is also recommended in patients with syncope, seizure, or nocturnal agonal respiration, after noncardiac causes of these symptoms have been carefully ruled out.[3] Needless to say, the ECG recording during syncope is the only convincing way to rule in or out VT during syncope, and only clinical judgment can be used to guide diagnostic and therapeutic decisions. However, in patients with Brugada syndrome, there is an abnormal regulatory imbalance of the autonomic nervous system that may be a common denominator to both syncope and ventricular fibrillation.

Limitations

The control subjects were significantly younger than patients with Brugada ECG or those with suspected NMS. However, it is reported that the positive rate of NTG-Tilt in the elderly was comparable to that seen in younger subjects.[21] Therefore, lower incidence of positive rate of the HUT test in the control subjects than that in the other 2 groups was not due to the relevant difference of age. The incidence of spontaneous type 1 ECG and the positive rate of the HUT test are smaller in Brugada patients with syncope episodes only than in those with documented VT or asymptomatic patients; however, statistical significance was not observed between the 3 groups.

Conclusions

Thirty-five percent of patients with Brugada ECG showed vasovagal responses during the HUT test. The HUT test was also positive in 41% among only Brugada patients with documented VT or no symptoms. During vasovagal response, ST-segment augmentation in the right precordial leads was observed in 69% of the HUT-positive Brugada patients, but no ventricular arrhythmias were induced. These data suggest that some Brugada patients have impaired balance of autonomic nervous system, which may relate to their syncopal episodes. Additional studies including a large number of subjects are needed to validate our findings and possibly evaluate the role of the HUT test in risk stratification of patients with Brugada ECG.

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An international compendium of mutations in the *SCN5A*-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing

Jamie D. Kapplinger, BA[*,1], **David J. Tester, BS**[*,1], **Marielle Alders, PhD**[†], **Begoña Benito, MD**[‡], **Myriam Berthet, BA**[§,‖], **Josep Brugada, MD, PhD**[¶], **Pedro Brugada, MD, PhD**[#], **Véronique Fressart, MD**[§,‖,**], **Alejandra Guerchicoff, PhD**[††], **Carole Harris-Kerr, PhD**[‡‡], **Shiro Kamakura, MD, PhD**[§§], **Florence Kyndt, PhD**[‖‖,¶¶,##], **Tamara T. Koopmann, PhD**[***], **Yoshihiro Miyamoto, MD**[†††], **Ryan Pfeiffer, BS**[††], **Guido D. Pollevick, PhD**[‡‡], **Vincent Probst, MD, PhD**[‖‖,##], **Sven Zumhagen, MD**[‡‡‡], **Matteo Vatta, PhD**[§§§], **Jeffrey A. Towbin, MD**[‖‖‖], **Wataru Shimizu, MD, PhD**[§§], **Eric Schulze-Bahr, MD**[‡‡‡], **Charles Antzelevitch, PhD**[††], **Benjamin A. Salisbury, PhD**[‡‡], **Pascale Guicheney, PhD**[§,‖,**], **Arthur A. M. Wilde, MD, PhD**[***], **Ramon Brugada, MD, PhD**[¶¶¶], **Jean-Jacques Schott, PhD**[‖‖,¶¶,###], and **Michael J. Ackerman, MD, PhD**[*]

[*]Departments of Medicine, Pediatrics, and Molecular Pharmacology and Experimental Therapeutics/Divisions of Cardiovascular Diseases and Pediatric Cardiology, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota [†]Department of Clinical Genetics, Academic Medical Centre, Amsterdam, the Netherlands [‡]Departamento de Biotecnología, Universidad Politécnica de Madrid, Madrid, Spain [§]Inserm, U956, Groupe Hospitalier Pitié-Salpêtrière, Paris, France [‖]UPMC Univ Paris 06, UMR-S956, IFR14, Paris, France [¶]Hospital Clínic, University of Barcelona, Barcelona, Spain [#]Heart Rhythm Management Centre, Cardiovascular Institute, UZ Brussel, VUB Brussels, Brussels, Belgium [**]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de Biochimie, Unité de Cardiogénétique et Myogénétique, Paris, France [††]Masonic Medical Research Laboratory, Utica, New York [‡‡]PGxHealth, LLC, a division of Clinical Data, Inc., New Haven, Connecticut [§§]Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan [‖‖]Institut National de la Sante et de la Recherche Medicale, UMR 915, F-44000 Nantes, France [¶¶]CNRS ERL3147, F-44000 Nantes, France [##]Service de Cardiologie, L'Institut du Thorax Centre Hospitalier Universitaire de Nantes, F-44000 Nantes, France [***]Heart Failure Research Centre, Department of Cardiology, Academic Medical Centre, Amsterdam, the Netherlands [†††]Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan [‡‡‡]Genetics of Heart Diseases, Hospital of the University of Münster, Germany [§§§]Department of Pediatrics (Cardiology) and Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas [‖‖‖]The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio [¶¶¶]Cardiovascular Genetics Center, School of Medicine, University of Girona, Spain [###]Faculté de Médecine, L'Institut du Thorax, Université de Nantes, F-44000 Nantes, France

Abstract

Address reprint requests and correspondence: Dr. Michael J. Ackerman, Windland Smith Rice Sudden Death Genomics Laboratory, Guggenheim 501, Mayo Clinic, Rochester, Minnesota 55905. ackerman.michael@mayo.edu..

[1]Mr. Kapplinger and Mr. Tester contributed equally to this work.