Table 3. Probability of Sudden Death or VF During Follow-Up Depending on Clinical and Electrophysiological Variables in All Probands (Type 1 and Non–Type 1 Groups)

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Prior VF	21.46	8.00–57.53	<0.0001	17.48	6.22–49.11	<0.0001
FH of SCD	6.35	2.84–14.19	<0.0001	3.28	1.42–7.60	0.005
Inferolateral ER	4.14	1.71–10.00	0.001	2.66	1.06–6.71	0.03
AF	2.15	0.92–5.03	0.07	0.87	0.36–2.09	0.75
Syncope	0.35	0.08–1.09	0.15			
Sp. type1	2.31	0.67–7.94	0.18			
VF induc. (apex/OT)	1.81	0.72–4.70	0.20			
VF induc. (apex)	1.58	0.60–4.11	0.34			
Male		NA				

FH indicates family history; inferolateral ER, inferolateral early repolarization; AF, atrial fibrillation; Sp. type 1, spontaneous type 1 ST-elevation on 12-lead ECG at baseline; VF induc. (apex/OT), VF induction by programmed pacing at the RV apex or RV outflow tract; and VF induc. (apex), VF induction by programmed pacing at the RV apex.

recorded only at the higher leads V_1 and V_2 showed a prognosis similar to that of men with a type 1 ECG when using standard leads. In the past, patients with non–type 1 ST-elevation in standard ECG had been excluded from studies as a benign entity of Brugada syndrome. However, if patients had a history of aborted sudden death or agonizing nocturnal dyspnea, non–type 1 Brugada-pattern ECG should not be disregarded. Careful follow-up including ECG recording at the higher intercostals spaces and the implantation of ICD is probably required in such a patient to prevent SCD.

Clinical Features of Probands With Non–Type 1 ECG

The clinical profiles of probands were very similar between the non–type 1 group and the type 1 group (Table 2). Inferolateral early repolarization occurred equally in small percentage of patients in both groups (8% and 11%, respectively), which is comparable to the prevalence (12%) of early repolarization that Letsas et al[17] reported in patients with Brugada syndrome. This means that the patient characteristics of the non–type 1 group are much closer to Brugada syndrome than early repolarization syndrome reported by Haïssaguerre et al,[9] in which the VF occurrence rate during sleeping was low (19%) and VF inducibility by EPS was only 34%. Moreover, they reported that several aspects including the relapsing VF and the efficacy of isoproterenol and quinidine,[9,18] which were observed in some patients with early repolarization, were exactly like those of typical Brugada syndrome. Haïssaguerre et al[9] excluded patients with Brugada syndrome, defined as right bundle-branch block and ST-segment elevation >0.2mV in leads V_1–V_3, at the enrollment. However, considering that they possibly included patients with non–type 1 ECG as non-Brugada pattern in their study, some patients with prior VF and early repolarization might have represented non–type 1 Brugada patients of high risk.

Predictors of Outcome

It was reported that male sex, a previous episode of syncope, a spontaneous type 1 ECG, and inducibility of ventricular arrhythmias by EPS are predictors for poor outcome.[2–4] Brugada et al demonstrated that inducibility of ventricular arrhythmias was a reliable marker in patients with and without VF/SCD,[2,4] although Priori et al[3] did not find any significant difference in the analysis of all patients. A spontaneous type 1 ECG was also indicated as a reliable marker of poor prognosis by Brugada et al[4] in the analysis of patients without VF/SCD and by Eckardt et al[5] in all patients.[5] However, we could not find any reliability in these markers (Figures 3 and 5). Inducibility of ventricular arrhythmias was not a significant predictor even if it was evaluated by programmed pacing only from the RV apex (type 1 group: HR, 1.9 [95% CI, 0.7 to 5.2], $P=0.18$; all probands: HR, 1.5 [95% CI, 0.6 to 4.1], $P=0.34$, by univariate analysis).

In contrast, a family history of SCD occurring at age of <45 years is an independent risk factor of a poor prognosis in probands of any groups irrespective of their ECG type (type 1 or non–type 1) or symptoms (with VF or without VF). This was probably caused by a smaller proportion of probands with a family history of SCD as compared with previous studies[2–5] A family history was not found to be a marker in studies that enrolled many patients with SCD or a family history of Brugada syndrome. These results indicate that we should evaluate risks for arrhythmic events cautiously in studies with a significant number of family members.

Early repolarization pattern in the inferolateral leads was another indicator of poor prognosis, although Letsas et al[17] did not find any association with arrhythmic events in the data collected from 3 European centers, which also included ≈30% of patients with a family history of SCD. The reason for the poor outcome in probands with early repolarization in this study is not clear. However, it is conceivable that the combination of precordial Brugada-pattern ST-elevation with inferolateral early repolarization may represent electric heterogeneity in extensive regions of ventricles, which can result in lethal ventricular arrhythmias.

Study Limitations

In this study, premature ventricular electric stimulation was given until refractoriness was reached. The minimal

coupling interval of extrastimuli was not constant between participating hospitals and was sometimes shortened to <200 ms to induce ventricular arrhythmias.

We did not show the results of genetic analysis in this report, although more than half of the patients underwent genetic screening. Detailed results will be presented in a future report. So far, no positive relationship between genetic findings and patient outcomes has been found.[3,19]

We did not record ECGs at the higher intercostals spaces systematically except for probands with cardiac events, because the importance of "high-recording" became apparent in the course of this study.[6] Therefore, some patients of the non–type 1 group may have shown type 1 ST-elevation at the higher precordial positions.

Conclusions

This study described the long-term prognosis of probands with noncoved (non–type 1) Brugada-pattern ECG compared with type 1 ECG. The annual incidence of fatal arrhythmic events was similar between the 2 groups, which reached 10.6% in probands with non–type 1 ECG and a prior episode of VF. A family history of SCD occurring at age of <45 years and the presence of early repolarization were indicators of poor outcome although VF inducibility and a spontaneous type 1 ST-elevation were not reliable indicators in this prospective study including only probands.

Appendix

The following investigators and institutions participated in this study: A. Hukui, Yamagata University, Yamagata; M. Hiraoka, Tokyo Dental and Medical University, Tokyo; S. Takata, Kanazawa University, Kanazawa; H. Sakurada, Hiroo Metropolitan Hospital, Tokyo; Y. Eki, Ibaragi-higashi National Hospital, Tokai; Y. Sasaki, Nagano National Hospital, Ueda; Y. Tomita, Nagoya Medical Center, Nagoya; U. Shintani, Mie-chuo Medical Center, Tsu; T. Hashizume, Minami-Wakayama Medical Center, Tanabe; Y. Fujimoto, Okayama Medical Center, Okayama; W. Matsuura, Higashihiroshima Medical Center, Higashihiroshima; K. Sakabe, Zentuuji National Hospital, Zentuuji; and I. Matsuoka, Kagoshima Medical Center, Kagoshima, Japan.

Sources of Funding

This work was supported by a research grant for cardiovascular diseases (13A-1, 16C-3) from the Ministry of Health, Labor, and Welfare of Japan.

Disclosures

None.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol*. 1992;20:1391–1396.
2. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation*. 2002;105:73–78.
3. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation*. 2002;105:1342–1347.
4. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation*. 2003;108:3092–3096.
5. Eckardt L, Probst V, Smits JP, Bahr ES, Wolpert C, Schimpf R, Wichter T, Boisseau P, Heinecke A, Breithardt G, Borggrefe M, LeMarec H, Bocker D, Wilde AA. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation*. 2005;111:257–263.
6. Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. *J Cardiovasc Electrophysiol*. 2000;11:396–404.
7. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation*. 2002;106:2514–2519.
8. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde AA. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;111:659–670.
9. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023.
10. Hattori Y, Inomata N. Modes of the Na channel blocking action of pilsicainide, a new antiarrhythmic agent, in cardiac cell. *Japan J Pharmacol*. 1992;58:365–373.
11. Morita H, Morita ST, Nagase S, Banba K, Nishii N, Tani Y, Watanabe A, Nakamura K, Kusano KF, Emori T, Matsubara H, Hina K, Kita T, Ohe T. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. *J Am Coll Cardiol*. 2003;42:1624–1631.
12. Letsas KP, Efremidis M, Gavielatos G, Filippatos GS, Sideris A, Kardaras F. Neurally mediated susceptibility in individuals with Brugada-type ECG pattern. *Pacing Clin Electrophysiol*. 2008;31:418–421.
13. Nademanee K, Veerakul G, Nimmannit S, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S, Tatsanavivat P. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation*. 1997;96:2595–2600.
14. Bezzina CR, Shimizu W, Yang P, Koopmann TT, Tanck MWT, Miyamoto Y, Kamakura S, Roden DM, Wilde AA. Common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction. *Circulation*. 2006;113:338–344.
15. Sacher F, Probst V, Iesaka Y, Jacon P, Laborderie J, Mizon-Gérard F, Mabo P, Reuter S, Lamaison D, Takahashi Y, O'Neill MD, Garrigue S, Pierre B, Jaïs P, Pasquié JL, Hocini M, Salvador-Mazenq M, Nogami A, Amiel A, Defaye P, Bordachar P, Boveda S, Maury P, Klug D, Babuty D, Haïssaguerre M, Mansourati J, Clémenty J, Le Marec H. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation*. 2006;114:2317–2324.
16. Miyamoto K, Yokokawa M, Tanaka K, Nagai T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Shimizu W. Diagnostic and prognostic value of a type 1 Brugada electrocardiogram at higher (third or second) V1 to V2 recording in men with Brugada syndrome. *Am J Cardiol*. 2007;99:53–57.
17. Letsas KP, Sacher F, Probst V, Weber R, Knecht S, Kalusche D, Haïssaguerre M, Arentz T. Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome. *Heart Rhythm*. 2008;5:1685–1689.
18. Haïssaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P.

Clémenty J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization: role of drug therapy. *J Am Coll Cardiol*. 2009;53:612–619.

19. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, Morita H, Nishii N, Watanabe A, Tada T, Murakami M, Miyaji K, Hiramatsu S, Nakagawa K, Tanaka M, Miura A, Kimura H, Fuke S, Sumita W, Sakuragi S, Urakawa S, Iwasaki J, Ohe T. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol*. 2008;51:1176–1180.

CLINICAL PERSPECTIVE

The prognosis of patients with saddleback or noncoved type (non–type 1) ST-elevation in Brugada syndrome is unknown. We compared the long-term prognosis of 85 probands with non–type 1 ECG with 245 probands with coved (type 1) Brugada-pattern ECG prospectively. The absence of type 1 ECG was confirmed by drug provocation test and multiple recordings. Clinical profiles and outcomes did not differ between the non–type 1 and type 1 groups. The annual rate of fatal arrhythmic events was very low in asymptomatic probands and those with syncope but was higher in probands with ventricular fibrillation. A family history of sudden cardiac death at age <45 years and the presence of inferolateral early repolarization were indicators of poor prognosis, although ventricular fibrillation inducibility and a spontaneous type 1 ST-elevation were not reliable parameters in this prospective study including only probands.

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

Dr. W. Shimizu was supported by the Health Sciences Research Grants (H18—Research on Human Genome—002) and the Research Grant for the Cardiovascular Diseases (21C-8) from the Ministry of Health, Labor, and Welfare of Japan.

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

Manuscript received 18 April 2009; Revised manuscript received 30 July 2009; Accepted for publication 3 August 2009.

doi: 10.1111/j.1540-8167.2009.01599.x

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 ($\geq$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] $\times$ 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 $\pm$ 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 $\times$ 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]

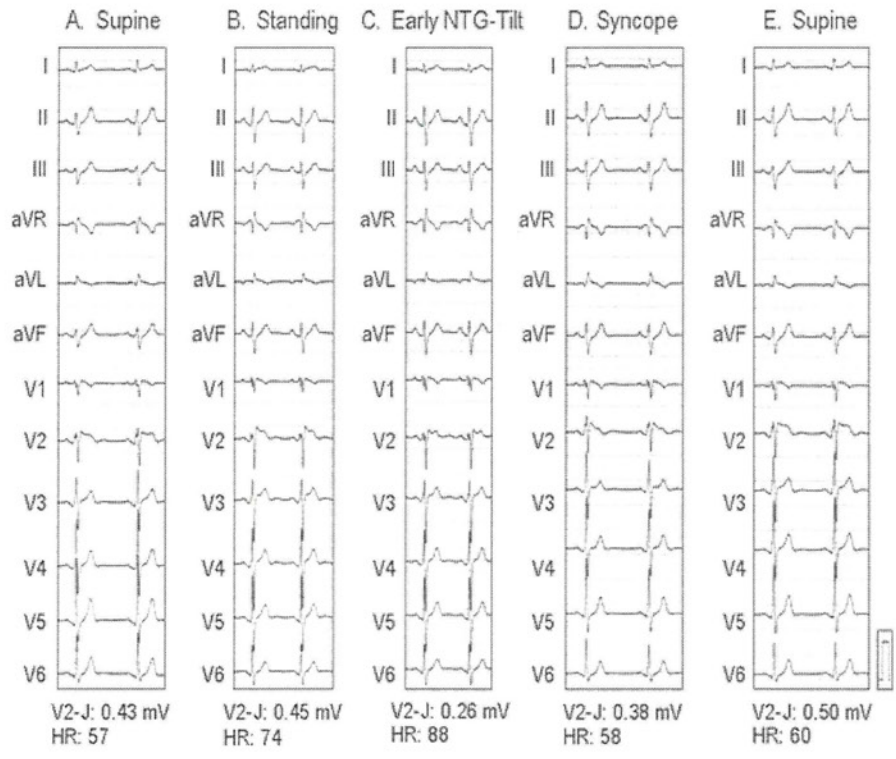

Figure 1. *The12-leads electrocardiogram (ECG) during head-up tilt test in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada ECG at supine position (A), at standing position (B), at early phase of NTG-Tilt (C), at syncope (D), and at supine position following syncope (E). 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).*

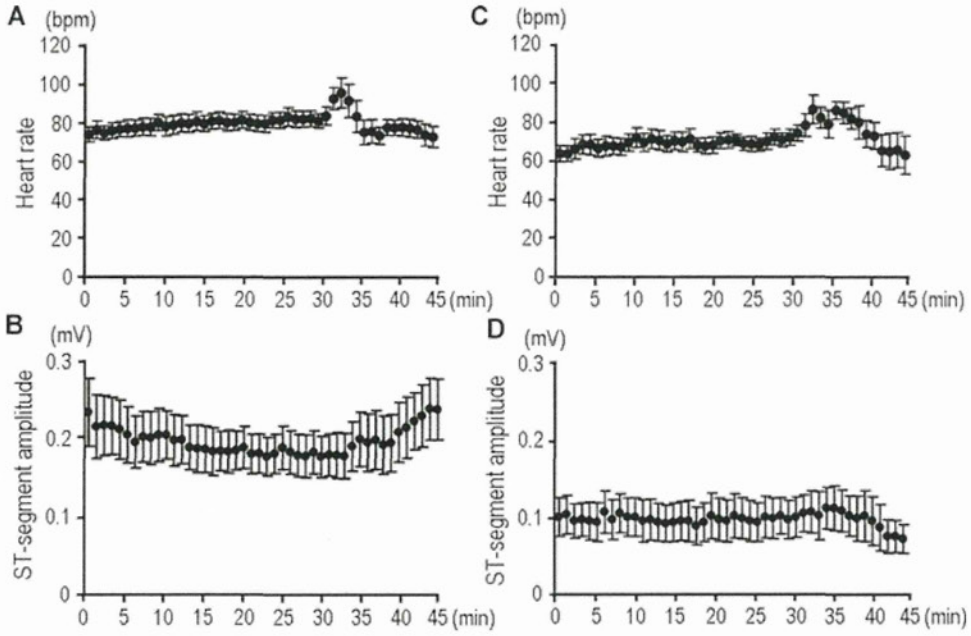

Figure 2. *Response of the heart rate and ST-segment amplitude during the head-up tilt (HUT) test in 16 HUT-positive patients with Brugada electrocardiogram (ECG) (A, B) and in 10 HUT-positive patients with suspected neurally mediated syncope (NMS) (C, D). At first, the passive tilt (Control-Tilt) was 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).*

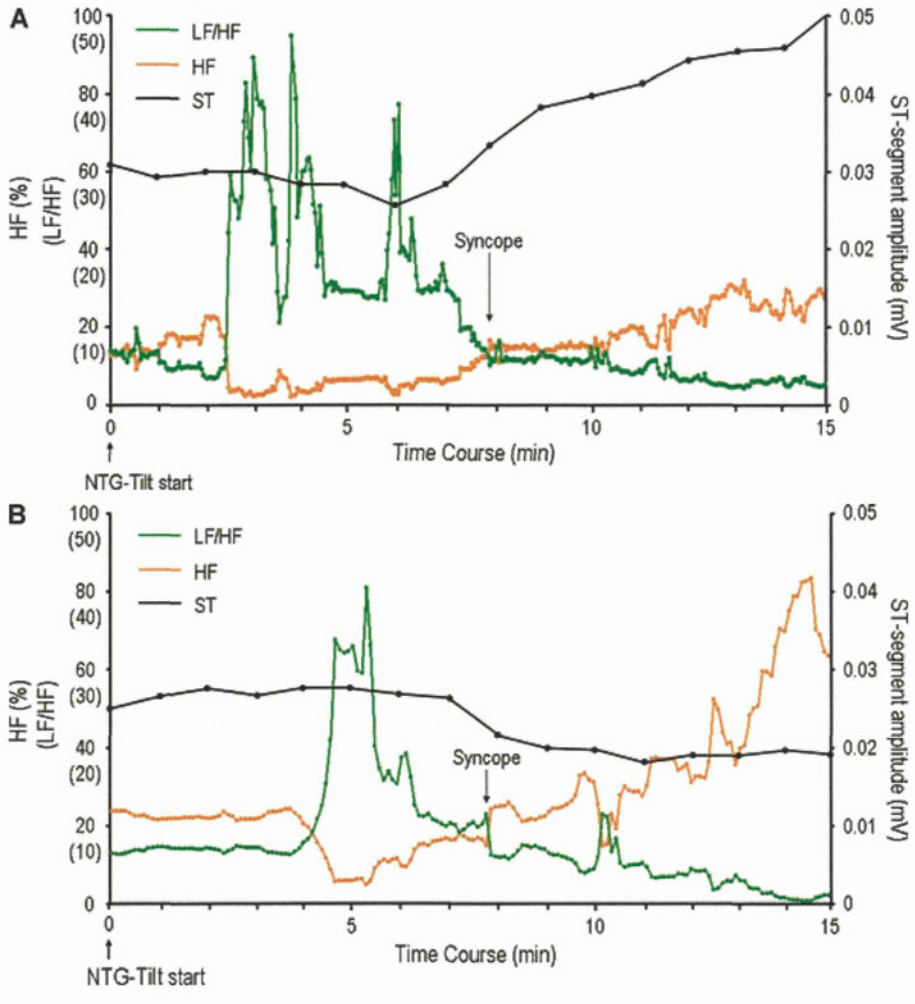

Figure 3. *Autonomic responses during head-up tilt (HUT) test. The autonomic activities in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada electrocardiogram (ECG) (A) and those in a representative NTG-Tilt-positive patient with suspected NMS (B). Before tilt-induced syncope, 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.

References

1. Brugada P, Brugada J: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391-1396.
2. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA, Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology: Proposed diagnostic criteria for the Brugada syndrome: Consensus report. Circulation 2002;106:2514-2519.
3. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A: Brugada syndrome: Report of the second consensus conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659-670.
4. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Moya A, Raviele A, Sutton R, Theodorakis G, Wieling W, Task Force on Syncope, European Society of Cardiology: Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001;22:1256-1306.
5. Nowak L, Nowak FG, Janko S, Dorwarth U, Hoffmann E, Botzenhardt F: Investigation of various types of neurocardiogenic response to head-up tilting by extended hemodynamic and neurohumoral monitoring. Pacing Clin Electrophysiol 2007;30:623-630.
6. Dalla PR, Kleinmann A, Zysk S, Bechtold S, Netz N: Head-up-tilt testing in children: New perspectives using beat-to-beat blood-pressure monitoring. Images Paediatr Cardiol 2005;22:1-7.
7. Boysen A, Lewin MA, Hecker W, Leichter HE, Uhlemann F: Autonomic function testing in children and adolescents with diabetes mellitus. Pediatr Diabetes 2007;8:261-264.
8. Yamasaki F, Sato T, Sugimoto K, Takata J, Chikamori T, Sasaki M, Doi Y: Effect of diltiazem on sympathetic hyperactivity in patients with vasospastic angina as assessed by spectral analysis of arterial pressure and heart rate variability. Am J Cardiol 1998;81:137-140.
9. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E: Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178-193.
10. Márquez MF, Rivera J, Hermosillo AG, Iturralde P, Colín L, Moragrega JL, Cárdenas M: Arrhythmic storm responsive to quinidine in a patient with Brugada syndrome and vasovagal syncope. Pacing Clin Electrophysiol 2005;28:870-873.
11. Patruno N, Pontillo D, Anastasi R, Sunseri L, Giamundo L, Ruggeri G: Brugada syndrome and neurally mediated susceptibility. Ital Heart J 2005;6:761-764.

12. Samniah N, Iskos D, Sakaguchi S, Lurie KG, Benditt DG: Syncope in pharmacologically unmasked Brugada syndrome: Indication for an implantable defibrillator or an unresolved dilemma? Europace 2001;3:159-163.
13. Wichter T, Matheja P, Eckardt L, Kies P, Schäfers K, Schulze-Bahr E, Haverkamp W, Borggrefe M, Schober O, Breithardt G, Schäfers M: Cardiac autonomic dysfunction in Brugada syndrome. Circulation 2002;105:702-706.
14. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S: Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95:2277-2285.
15. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, Taguchi A, Suyama K, Kamakura S, Shimomura K: The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J 1999;20:465-470.
16. Scornik FS, Desai M, Brugada R, Guerchicoff A, Pollevick GD, Antzelevitch C, Pérez GJ: Functional expression of "cardiac-type" Nav1.5 sodium channel in canine intracardiac ganglia. Heart Rhythm 2006;3:842-850.
17. Makita N, Sumitomo N, Watanabe I, Tsutsui H: Novel SCN5A mutation (Q55X) associated with age-dependent expression of Brugada syndrome presenting as neurally mediated syncope. Heart Rhythm 2007;4:516-519.
18. Grimster A, Segal OR, Behr ER. Type I Brugada electrocardiogram pattern during the recovery phase of exercise testing. Europace 2008;10:897-898.
19. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S: Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061-1070.
20. Nishizaki M, Sakurada H, Mizusawa Y, Niki S, Hayashi T, Tanaka Y, Maeda S, Fujii H, Ashikaga T, Yamawake N, Isobe M, Hiraoka M. Influence of meals on variations of ST segment elevation in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2008;19:62-68.
21. Tan MP, Parry SW: Vasovagal syncope in the older patient. J Am Coll Cardiol 2008;51:599-606.

厚生労働省科学研究補助金
医療技術実用化総合研究事業

平成２０年度～平成２４年度
総合研究報告書

慢性心不全の予後を改善するための非侵襲で安全・安心な無痛性ICDの実用化臨床試験
（Ｈ２０－活動－指定－００７）

主任研究者：砂川　賢二
（九州大学大学院医学研究院）

Vol. 2

平成２５（２０１３）年５月

厚生労働省科学研究補助金
医療技術実用化総合研究事業

平成２０年度～平成２４年度
総合研究報告書

慢性心不全の予後を改善するための非侵襲で安全・安心な無痛性ICDの実用化臨床試験
（Ｈ２０－活動－指定－００７）

主任研究者：砂川　賢二
（九州大学大学院医学研究院）

Vol. 2

平成２５（２０１３）年５月

目　　次
Vol. 2

QRS Prolongation is Associated With High Defibrillation Thresholds During Cardioverter-Defibrillator Implantations in Patients With Hypertrophic Cardiomyopathy

Takayuki Nagai, MD; Takashi Kurita, MD; Kazuhiro Satomi, MD; Takashi Noda, MD; Hideo Okamura, MD; Wataru Shimizu, MD; Kazuhiro Suyama, MD; Naohiko Aihara, MD; Junjiro Kobayashi, MD*; Shiro Kamakura, MD

Background: Although high defibrillation threshold (DFT) is a major and unavoidable clinical problem after implantation of an implantable cardioverter defibrillator (ICD), little is known about the cause and management of a high DFT in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to assess the predictors of a high DFT in patients with HCM.

Methods and Results: Twenty-three patients with non-dilated HCM who underwent ICD implantation were included. The DFT at the time of the device implantation was measured in all patients. The patients were divided into 2 groups, a high DFT group (DFT ≥15J, n=13) and a low DFT group (DFT <15J, n=10); and their baseline characteristics were compared. The QRS duration was longer in the high than in the low DFT group (128±31 vs 103±12 ms, respectively; P=0.02). QRS duration, left ventricular (LV) end-systolic diameter, and LV ejection fraction were significant predictors of DFT in univariate analysis. However, in multivariate analysis, the only factor significantly associated with DFT was QRS duration (P=0.002).

Conclusions: QRS duration is the most consistent predictor of a high DFT in HCM patients undergoing ICD implantation. (*Circ J* 2009; **73:** 1028–1032)

Key Words: Defibrillation threshold; Hypertrophic cardiomyopathy; Implantable cardioverter defibrillator; QRS prolongation

A subgroup of patients with hypertrophic cardiomyopathy (HCM) is at a high risk of having ventricular tachycardia and/or ventricular fibrillation. The implantable cardioverter-defibrillator (ICD) is widely recognized as the most effective and essential therapy for this patient population[1–3] It has been demonstrated that both appropriate and inappropriate ICD discharges are frequently observed in HCM patients[1–3] and this might impair quality-of-life as well as reduce battery longevity. Class III antiarrhythmic agents such as amiodarone have the potential for reducing ICD shocks[4] and might improve patients' prognosis. Furthermore, class I agents are also used in HCM patients to control atrial fibrillation or reduce the pressure gradient in the left ventricular (LV) outflow tract or mid-ventricle when an obstruction is present[5–7] The combined use of antiarrhythmic agents and an ICD in patients with HCM, and the larger volume of myocardium (caused by hypertrophy of the left ventricle) might result in a high defibrillation threshold (DFT). However, the predictors of a high DFT in patients with HCM have not been fully characterized. Thus, the purpose of this retrospective study was to evaluate the factors causing a high DFT in patients with HCM and ventricular tachycardia/ventricular fibrillation.

(Received July 31, 2008; revised manuscript received January 7, 2009; accepted January 15, 2009; released online April 10, 2009)
*Division of Cardiology, Department of Internal Medicine, *Department of Cardiovascular Surgery, National Cardiovascular Center, Suita, Japan*
Mailing address: Takashi Kurita, MD, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: kuritat@hsp.ncvc.go.jp

Methods

Study Subjects

The study population consisted of 23 consecutive patients with an established diagnosis of HCM who underwent initial implantation of an ICD with a standard transvenous lead system at the National Cardiovascular Center from 1997 through to 2005. ICDs were implanted for secondary prevention in 20 of 23 patients, defined by clinical sustained ventricular tachyarrhythmia or resuscitation from sudden cardiac death. HCM was diagnosed on the basis of echocardiographic criteria defined as the presence of LV hypertrophy in the absence of other causes of hypertrophy. These patients also met the definition and classification proposed by the 1995 World Health Organization/International Society and Federation of Cardiology Task Force[8] All defibrillation leads were implanted by a left cephalic vein cutdown and positioned in the right ventricular apex. No patient had any prior pacemaker implantation, and 2 had permanent atrial fibrillation. Patients who were diagnosed with HCM who progressed to a dilated phase of HCM were excluded from the study.

ICD Implantation and DFT Testing

The following ICD models were implanted: 7220C (n=1), 7223Cx (n=6), 7227Cx (n=2), 7229Cx (n=5), 7271Cx (n=1), and 7273Cx (n=5), manufactured by Medtronic, Inc (Minneapolis, MN, USA); and the 1861 (n=3) manufac-

Table 1. Patient Characteristics

	Defibrillation threshold		P value
	<15J (n=10)	≥15J (n=13)	
Gender (M/F)	7/3	9/4	NS
Age, years	52±18	54±16	NS
Height, cm	163±8	162±8	NS
Body weight, kg	55±9	59±7	NS
QRS duration, ms	103±12	128±31	0.02
LV ejection fraction, %	68±16	58±10	0.09
Defibrillation threshold, J	10±0.4	18±5	0.0001
Antiarrhythmic agents, n (%)	3 (30)	6 (46)	NS
Amiodarone, n (%)	2 (20)	4 (31)	NS
Disopyramide, n (%)	1 (10)	1 (8)	NS
Mexiletine, n (%)	0 (0)	2 (15)	NS
Single coil lead system, n (%)	9 (90)	8 (62)	NS

Data are mean±SD.
NS, not significant; LV, left ventricular.

Table 2. Echocardiographic Measurements

	Defibrillation threshold		P value
	<15J (n=10)	≥15J (n=13)	
LV end-diastolic diameter, mm	39±6	42±6	NS
LV end-systolic diameter, mm	22±6	26±5	0.048
Interventricular septal thickness, mm	17±5	18±6	NS
LV posterior wall thickness, mm	13±3	14±8	NS
LV mass, g	286±124	369±211	NS
LV mass index, g/m^2	178±64	227±126	NS

Data are mean±SD.
Abbreviations see in Table 1.

tured by Guidant Corp (St. Paul, MN, USA). All ICD systems used biphasic waveforms. A single-coil transvenous lead system was utilized in 17 patients and a dual-coil system was used in 6 patients. All implant procedures were performed under general anesthesia using propofol in the operating room. At the end of the ICD implantation after ventricular fibrillation was induced using a T-wave shock or 50-Hz burst pacing, DFT was measured using a step-down method from an initial delivered energy of 15J with decrements of 5J[9,10] If the initial 15J shock failed, the energy was increased in 5J steps until defibrillation was successful. A 5-min interval was allowed between inductions and defibrillations of ventricular fibrillation. The DFT was defined as the lowest delivered energy shock that resulted in a successful defibrillation. According to the mean value of DFT (14±5J), the patients were classified into 10 patients with a low DFT (<15J) and 13 patients with a high DFT (≥15J).

Variables Assessed

The following variables were used for analysis: sex, age, height, body weight, QRS duration, LV ejection fraction quantified by radionuclide ventriculography or LV cineangiography, the use of amiodarone or class I antiarrhythmic drugs, utilization of a single-coil transvenous lead system, echocardiographic parameters including the LV end-diastolic and end-systolic diameters, interventricular septal thickness, LV posterior wall thickness, LV mass calculated from echocardiographic data by standard formulas[11,12] and LV mass index (dividing the LV mass by the body surface area). The QRS duration was defined as the maximal QRS length in any lead measured manually from the first to the last sharp deflection crossing the isoelectric line using standard resting 12-lead ECG (sweep speed, 25 mm/s and 1 mV/cm standardization). The average values of QRS duration that were obtained from 2 independent investigators blinded to each other's results were used (interobserver correlation for QRS duration was 0.941).

Statistical Analysis

The results are presented as percentages or the mean±SD, as appropriate. Several parameters in the 2 groups were compared with an unpaired Student's t-test. Categorical variables were compared using a Fisher's exact test. Linear regression analysis was used to determine the relationship between DFT and QRS duration. The variables with a P value <0.10 were entered into a multiple linear regression analysis to identify the independent predictors of DFT. The level of statistical significance was set at a P value <0.05.

Results

Twenty-three patients (16 men; mean age 53±17 years, range 16–77 years) were included in the analysis. None of the patients had any extreme hypertrophy (≥30 mm), and 4 patients were found to have significant LV outflow obstruction (≥30 mmHg) at rest by continuous Doppler echocardiography. The mean LV ejection fraction was 62±13%. Indications for an ICD implantation were primary prevention in 3 patients, ventricular tachycardia in 4 patients and aborted sudden cardiac death in 16 patients. At the time of device implantation, 6 patients were being treated with amiodarone (200 mg/day), 2 with sotalol and 4 with class I antiarrhythmic agents (disopyramide and mexiletine). No patient showed evidence of abnormalities in serum electrolyte concentrations and/or in acid–base equilibrium at the device implantation stage.

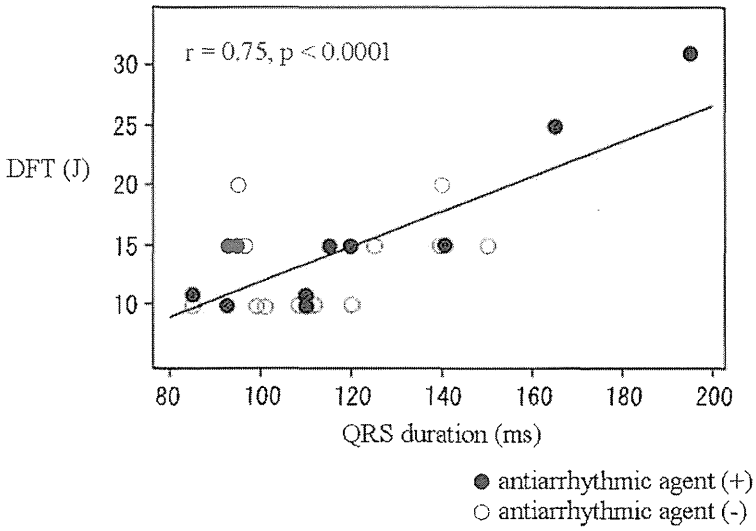

Figure. Relationship between QRS duration and DFT. The QRS duration demonstrated a modest positive correlation with the DFT at the time of the device implantation. DFT, defibrillation threshold.

The ICDs were implanted without any complications, and the induction and termination of the ventricular fibrillation were successful in all patients. The DFT (energy delivered) ranged from 10J to 31J (10 patients, 10–14J; 9 patients, 15–19J; 2 patients, 20–24J; 2 patients, 25–31J). The DFTs in patients treated with amiodarone (6 patients), combined amiodarone and a class I antiarrhythmic agent (mexiletine) (1 patient), class I antiarrhythmic agents (3 patients), and sotalol (2 patients) were 16±9J, 15J, 17±7J, and 13±3J, respectively. An unacceptably high DFT (≥25J) was obtained in 2 patients who were receiving amiodarone (1 patient, 200mg/day) or mexiletine (1 patient, 450mg/day) at the time of the implantation (these 2 patients were included in the high DFT group). However, the DFT in these 2 patients decreased to a level with a 10J safety margin between the maximum shock energy of the ICD and the DFT after cessation of amiodarone (21J) or mexiletine (20J). Therefore, none of the patients required any additional use of a subcutaneous array or patch.

The baseline characteristics and echocardiographic measurements for the 2 groups are listed in **Tables 1** and **2**, respectively. The QRS duration was significantly longer in patients with a high than with a low DFT (128±31 vs 103±12ms, respectively; P=0.02). There was a trend toward a lower LV ejection fraction in the patients with a high DFT (P=0.09). The use of amiodarone and/or class I antiarrhythmic drugs did not differ between the 2 groups. As shown in **Table 2**, the LV end-systolic diameter was significantly smaller in those patients with a low than with a high DFT (22±6 vs 26±5mm, respectively; P=0.048). The LV mass and mass index exhibited no statistically significant difference between the 2 groups.

The QRS duration demonstrated a modest positive correlation with the DFT at the time of device implantation (r=0.75, P<0.0001) for the group as a whole (**Figure**). A multivariate analysis was performed on the 3 variables that had a P value <0.10 in the univariate analysis: QRS duration, LV end-systolic diameter, and LV ejection fraction. This analysis showed that QRS duration was the only independent predictor of DFT (P=0.002).

Discussion

In this study, we identified QRS duration as the only variable that was associated with a high DFT at the time of ICD implantation in patients with HCM. To the best of our knowledge, this is the first report to investigate the association between QRS duration and DFT in patients with HCM. Because of the pro-arrhythmic and/or negative inotropic effects of class I antiarrhythmic agents, the use of these drugs in patients with depressed LV function is contraindicated. Furthermore, class Ia antiarrhythmic drugs such as disopyramide or cibenzoline might lead to a rise in DFT by producing a wider zone between the resting membrane potential and threshold potential[13] However, class Ia antiarrhythmic agents have been regarded as part of the standardized therapy, not only for reducing LV pressure gradients[5–7] in patients with obstructive HCM, but also for improving LV diastolic dysfunction even in patients with non-obstructive HCM[14,15] Therefore, it is even more important to predict an increase in DFT before ICD implantation in patients with HCM. Previous studies have described several clinical factors that are associated with a high DFT, such as LV dilatation;[16] body size;[16] decreased LV ejection fraction;[17] administration of antiarrhythmic drugs (class I; flecainide;[18] mexiletine[19,20] etc, class III; amiodarone[21–23]), myocardial ischemia;[24–27] the ventricular fibrillation duration;[28,29] and LV mass[23,30,31] Among these factors possibly associated with high DFTs, only the LV ejection fraction was found to be a univariate predictor of a high DFT in the present study. This might be because HCM exhibits a unique structural and electrophysiologic substrate in the myocardium. Almquist et al reported that extreme LV hypertrophy (wall thickness >45mm) and the administration of amiodarone were related to a high DFT in patients with HCM[32] The LV mass index was slightly larger in the high than in the low DFT group in spite of the absence of any extreme LV hypertrophy in our series. Although this result was not statistically significant because of the small sample size, this suggests that a larger LV mass might increase the DFT.

QRS Duration and DFT

Although 2 published studies have shown an association between QRS duration and DFT, QRS duration was not an independent predictor of DFT in multivariate analysis[16,30] However, those study populations included mainly ischemic heart disease patients. This is the first study to investigate the association between QRS duration and DFT in patients

with HCM. Dhingra et al showed that QRS duration was positively related to LV mass and dimensions in individuals free of heart failure and myocardial infarction[33] However, there was no significant association between QRS duration and LV mass in our subjects. Asymmetric LV hypertrophy, which is frequently observed in HCM, might make it difficult to precisely evaluate LV mass in the clinical setting. This might be a possible explanation for our observed data.

Study Limitations

The results presented here must be viewed as preliminary as they are based on experience in a single center and in a small number of patients. Furthermore, this study was conducted retrospectively. In addition, we did not have any follow-up data on DFT after device implantation. All patients underwent the implantations under general anesthesia using propofol, as described above, which might have elevated the DFT[34] Thus, it is possible that the DFT in the operating room differed from that in the clinical setting. A further major limitation is the absence of a uniform strategy for the selection of lead systems and antiarrhythmic agents that could affect the DFT. Finally, 2 patients in this study who had unacceptably high DFTs obtained a 10-J safety margin after cessation of antiarrhythmic agents. Moreover, not all patients taking antiarrhythmic agents at the ICD implantation had their DFTs measured after discontinuation of antiarrhythmic agents. We report here that the QRS prolongation was associated with a high DFT at the time of ICD implantation in patients with HCM, leaving doubt as to how much the antiarrhythmic agents would affect high DFT and QRS prolongation. Additional studies in a larger patient population are needed to determine the impact of QRS duration on DFT, as well as the influence of antiarrhythmic agents on DFT, and the long-term consequences of an elevated DFT in HCM patients.

Clinical Implications

In patients with HCM, the presence of a QRS prolongation on the 12-lead ECG should raise concern about a high DFT at the time of ICD implantation, and those patients should be started at a higher energy level for DFT measurements using a high-output device to obtain an adequate safety margin for defibrillation. In the patients who have already been implanted with an ICD, antiarrhythmic agents, which might cause a high DFT, should be prescribed very carefully. Moreover, when QRS prolongation is present before drug administration, DFT testing is warranted after the initiation of drug therapy.

Conclusion

The present report revealed an association between the QRS duration and DFT at the time of ICD implantation in patients with HCM. This might provide an important insight into the link between simple 12-lead ECG markers and the energy requirements for successful defibrillation in patients with HCM.

References

1. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000; **342:** 365–373.
2. Maron BJ, Estes NA 3rd, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. *Circulation* 2003; **107:** 2872–2875.
3. Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 2003; **26:** 1887–1896.
4. Lee CH, Nam GB, Park HG, Kim HY, Park KM, Kim J, et al. Effects of antiarrhythmic drugs on inappropriate shocks in patients with implantable cardioverter defibrillators. *Circ J* 2008; **72:** 102–105.
5. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; **45:** 1251–1258.
6. Hamada M, Shigematsu Y, Ikeda S, Hara Y, Okayama H, Kodama K, et al. Class Ia antiarrhythmic drug cibenzoline: A new approach to the medical treatment of hypertrophic obstructive cardiomyopathy. *Circulation* 1997; **96:** 1520–1524.
7. Hamada M, Shigematsu Y, Inaba S, Aono J, Ikeda S, Watanabe K, et al. Antiarrhythmic drug cibenzoline attenuates left ventricular pressure gradient and improves transmitral Doppler flow pattern in patients with hypertrophic obstructive cardiomyopathy caused by midventricular obstruction. *Circ J* 2005; **69:** 940–945.
8. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation* 1996; **93:** 841–842.
9. Neuzner J, Liebrich A, Jung J, Himmrich E, Pitschner HF, Winter J, et al. Safety and efficacy of implantable defibrillator therapy with programmed shock energy at twice the augmented step-down defibrillation threshold: Results of the prospective, randomized, multicenter Low-Energy Endotak Trial. *Am J Cardiol* 1999; **83:** 34D–39D.
10. Rashba EJ, Olsovsky MR, Shorofsky SR, Kirk MM, Peters RW, Gold MR. Temporal decline in defibrillation thresholds with an active pectoral lead system. *J Am Coll Cardiol* 2001; **38:** 1150–1155.
11. Sahn DJ, DeMaria A, Kisslo J, Weyman A (the Committee on M-Mode Standardization of the American Society for Echocardiography). Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978; **58:** 1072–1083.
12. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977; **55:** 613–618.
13. Babbs CF. Alteration of defibrillation threshold by antiarrhythmic drugs: A theoretical framework. *Crit Care Med* 1981; **9:** 362–363.
14. Hamada M, Shigematsu Y, Hara Y, Suzuki M, Ohtsuka T, Hiasa G, et al. Antiarrhythmic drug, cibenzoline, can directly improve the left ventricular diastolic function in patients with hypertrophic cardiomyopathy. *Jpn Circ J* 2001; **65:** 531–538.
15. Hamada M, Aono J, Ikeda S, Watanabe K, Inaba S, Suzuki J, et al. Effect of intravenous administration of cibenzoline on left ventricular diastolic pressures in patients with hypertrophic cardiomyopathy: Its relationship to transmitral Doppler flow profiles. *Circ J* 2007; **10:** 1540–1544.
16. Gold MR, Khalighi K, Kavesh NG, Daly B, Peters RW, Shorofsky SR. Clinical predictors of transvenous biphasic defibrillation thresholds. *Am J Cardiol* 1997; **79:** 1623–1627.
17. Pinski SL, Vanerio G, Castle LW, Morant VA, Simmons TW, Trohman RG, et al. Patients with a high defibrillation threshold: Clinical characteristics, management, and outcome. *Am Heart J* 1991; **122:** 89–95.
18. Reiffel JA, Coromilas J, Zimmerman JM, Spotnitz HM. Drug-device interactions: Clinical considerations. *Pacing Clin Electrophysiol* 1985; **8:** 369–373.
19. Yoon MS, Han J. Electrophysiologic effects of mexiletine on normal and ischemic ventricles. *J Electrocardiol* 1982; **15:** 109–113.
20. Marinchak RA, Friehling TD, Kline RA, Stohler J, Kowey PR. Effect of antiarrhythmic drugs on defibrillation threshold: Case report of an adverse effect of mexiletine and review of the literature. *Pacing Clin Electrophysiol* 1988; **11:** 7–12.
21. Khalighi K, Daly B, Leino EV, Shorofsky SR, Kavesh NG, Peters RW, et al. Clinical predictors of transvenous defibrillation energy requirements. *Am J Cardiol* 1997; **79:** 150–153.
22. Pelosi F Jr, Oral H, Kim MH, Sticherling C, Horwood L, Knight BP, et al. Effect of chronic amiodarone therapy on defibrillation energy requirements in humans. *J Cardiovasc Electrophysiol* 2000; **11:** 741–743.
23. Kopp DE, Blakeman BP, Kall JG, Olshansky B, Kinder CA, Wilber DJ. Predictors of defibrillation energy requirements with nonepicardial lead systems. *Pacing Clin Electrophysiol* 1995; **18:** 253–260.

24. Anastasiou-Nana MI, Tsagalou EP, Charitos C, Siafakas KX, Drakos S, Terrovitis JV, et al. Effects of transient myocardial ischemia on the ventricular defibrillation threshold. *Pacing Clin Electrophysiol* 2005; **28:** 97–101.
25. Babbs CF, Paris RL, Tacker WA Jr, Bourland JD. Effects of myocardial infarction on catheter defibrillation threshold. *Med Instrum* 1983; **17:** 18–20.
26. Qin H, Walcott GP, Killingsworth CR, Rollins DL, Smith WM, Ideker RE. Impact of myocardial ischemia and reperfusion on ventricular defibrillation patterns, energy requirements, and detection of recovery. *Circulation* 2002; **105:** 2537–2542.
27. Walcott GP, Killingsworth CR, Smith WM, Ideker RE. Biphasic waveform external defibrillation thresholds for spontaneous ventricular fibrillation secondary to acute ischemia. *J Am Coll Cardiol* 2002; **39:** 359–365.
28. Strobel JS, Kenknight BH, Rollins DL, Smith WM, Ideker RE. The effects of ventricular fibrillation duration and site of initiation on the defibrillation threshold during early ventricular fibrillation. *J Am Coll Cardiol* 1998; **32:** 521–527.
29. Windecker S, Ideker RE, Plumb VJ, Kay GN, Walcott GP, Epstein AE. The influence of ventricular fibrillation duration on defibrillation efficacy using biphasic waveforms in humans. *J Am Coll Cardiol* 1999; **33:** 33–38.
30. Hodgson DM, Olsovsky MR, Shorofsky SR, Daly B, Gold MR. Clinical predictors of defibrillation thresholds with an active pectoral pulse generator lead system. *Pacing Clin Electrophysiol* 2002; **25:** 408–413.
31. Chapman PD, Sagar KB, Wetherbee JN, Troup PJ. Relationship of left ventricular mass to defibrillation threshold for the implantable defibrillator: A combined clinical and animal study. *Am Heart J* 1987; **114:** 274–278.
32. Almquist AK, Montgomery JV, Haas TS, Maron BJ. Cardioverter-defibrillator implantation in high-risk patients with hypertrophic cardiomyopathy. *Heart Rhythm* 2005; **2:** 814–819.
33. Dhingra R, Ho Nam B, Benjamin EJ, Wang TJ, Larson MG, D'Agostino RB Sr, et al. Cross-sectional relations of electrocardiographic QRS duration to left ventricular dimensions: The Framingham Heart Study. *J Am Coll Cardiol* 2005; **45:** 685–689.
34. Cohen TJ, Chengot T, Quan C, Peller AP. Elevation of defibrillation thresholds with propofol during implantable cardioverter-defibrillator testing. *J Invasive Cardiol* 2000; **12:** 121–123.

Repolarization Spatial-Time Current Abnormalities in Patients with Coronary Heart Disease

KUNIOMI OGATA,* AKIHIKO KANDORI,* YASUSHI WATANABE,† AKIHIRO SUZUKI,† KIMIO TANAKA,† YUJI OKA,† HIROSHI TAKAKI,‡ HIDEAKI KANZAKI,‡ SATOSHI NAKATANI,‡ KUNIO MIYATAKE,‡ SHIGEYUKI WATANABE,§ IWAO YAMAGUCHI,§ TSUYOSHI MIYASHITA,* and SHIRO KAMAKURA‡

From the *Advanced Research Laboratory, Hitachi Ltd., Higashi-Koigakubo, Kokubunji, Tokyo, Japan; †Hitachi General Hospital, Ibaraki, Japan; ‡National Cardiovascular Center, Osaka, Japan; and §Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan

Background: *Magnetocardiography (MCG) is a new technique for visualizing a current distribution in the myocardium. In recent years, current distribution parameters (CDPs) have been developed based on the distribution. The CDPs reflect spatial-time current abnormalities in patients with coronary heart disease (CHD). However, the criteria and scoring method of the abnormalities using CDPs are still controversial.*

Method: *We measured MCG signals for 101 normal controls and 56 CHD patients (single-, double-, and triple-vessel diseases) using a MCG system. The CDPs (maximum current vector [MCV], total current vector [TCV], current integral map, and current rotation) during ventricular repolarization were analyzed. To evaluate the CDPs that are effective in distinguishing between normal controls and CHD patients, the areas under the receiver operating characteristic curve (A_z) are calculated. Furthermore, the total scores ("0" to "4") of four CDPs with high A_z values are also calculated.*

Results: *MCV and TCV angles at the T-wave peak had the highest A_z value. Furthermore, TCV angular differences between the ST-T segment also had high A_z values. Using the four CDPs, the averaged total score for patients with triple-vessel disease was the highest ("2.67") compared to the other groups (normal controls: 0.53). Furthermore, based on the assumption that subjects with a total score over "1" were suspected of having CHD, sensitivity and specificity were 85.7% and 74.3%, respectively.*

Conclusion: *We concluded that the score and criteria using MCV and TCV during repolarization in CHD patients can reflect lesion areas and time changes of electrical activation dispersion due to ischemia. (PACE 2009; 32:516–524)*

magneticardiogram, coronary heart disease, cardiac electrical current

Introduction

The number of people throughout the world who die each year from coronary heart disease (CHD) is about 7 million and counting.[1] In Japan, more than 70,000 people have died of CHD, and this number has remained steady for the last decade.[2] Under the circumstances, several types of medical equipment that allow early diagnosis of CHD have been developed.[3–18]

The exercise-induced electrocardiogram (ECG)[3–5] with treadmill and ergometer exercise test helps to diagnose and assess the severity of CHD. This device can detect abnormal electrical potential changes in an exercise examination. Therefore, exercise-induced ECG is prevalent in an initial evaluation when CHD is suspected. However, some problems with this method include the burden on patients and the long time required for measurement.

The magnetocardiogram (MCG) is a new medical device that measures the weak magnetic field generated by the ionic current in the human heart.[6–11] It is a noninvasive technique that involves no contact with the human body. The MCG remains largely unaffected by other organs because permittivity of the human body is relatively constant. Therefore, the MCG is expected to be a useful system to detect the imperceptible changes in cardiac electrical activation that are caused by various heart diseases.

Some clinical research has been done based on magnetic field parameters (MFPs), which are calculated from MCG signals.[12,13] These MFPs are obtained from coordinates and amplitudes of maximum and minimum magnetic fields during the ventricular repolarization phase. Park et al. examined four MFPs during the ST to T-wave peak for 185 patients with ischemic syndrome.[12] Tolstrup et al. examined seven MFPs during the ST-T segment for 125 patients with chest pain.[13] These examinations showed that an MCG test using MFPs had high sensitivity and specificity for detection

Address for reprints: Kuniomi Ogata, Advanced Research Laboratory, Hitachi Ltd., 1-280 Higashi-Koigakubo, Kokubunji, Tokyo 185-8601, Japan. Fax: 81-42-327-7783; e-mail: kuniomi.ogata.fb@hitachi.com

Received August 20, 2007; revised March 13, 2008; accepted December 15, 2008.