The threshold value of 440 ms for the definition of a normal-range QTc in the present study was based on the diagnostic criteria for LQTS proposed by Schwartz et al. (12), which define a prolonged QTc interval as ≥450 ms in male patients and ≥460 ms in female patients. We chose to use a uniform approach by selecting 440 ms as the upper limit of normal rather than having separate phenotypic definitions for male and female patients. It should also be noted that 2.5% of infants and 10% to 20% of adults exceed this cutoff (21). Thus, the 440-ms value is not meant to suggest an LQTS diagnosis on its own.

Conclusions

The present study shows that patients with LQTS who exhibit normal-range QTc intervals constitute approximately 25% of the LQTS population and have a significantly lower risk for life-threatening events compared with phenotypically affected patients but also exhibit a significant increase in the risk of ACA or SCD compared with unaffected family members. Missense mutations in the transmembrane regions of the ion channels, mainly in patients with LQT1 and LQT3, were shown to identify patients with normal-range QTc intervals who have an increased risk for ACA or SCD. In contrast, increments in QTc duration were not shown to be significantly associated with increased risk for life-threatening events in this population. These findings suggest that: 1) risk assessment in phenotype-negative family members of LQTS probands should include genetic testing, because a positive genetic test result in a family member with a normal-range QTc interval implies an overall >10-fold increase in the risk for ACA or SCD compared with a negative test result in an unaffected family member; 2) genetic data may be used to identify phenotype-negative patients with LQTS who are at increased risk for fatal ventricular tachyarrhythmias independently of QTc duration; and 3) LQTS mutation–positive patients with normal-range QTc intervals who are identified as having increased risk for life-threatening events on the basis of genotype and mutation characteristics (i.e., LQT1 and LQT3 with transmembrane-missense mutations) should be carefully followed and receive a similar management strategy as phenotype-positive patients with LQTS, including avoidance of QT-prolonging medications (22), routine therapy with beta-blockers, and possibly implantable cardioverter-defibrillator therapy in those who remain symptomatic despite medical therapy. Conversely, patients with the lowest risk profile of already low risk, concealed LQTS (i.e., concealed LQT2 and non-transmembrane-missense LQT1 and LQT3) may represent the nominally near zero risk subpopulation(s) of LQTS in need of only preventative health recommendations such as QT drug avoidance.

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Key Words: corrected QT interval ▪ long-QT syndrome ▪ sudden cardiac death.

APPENDIX

For a table about *KCNQ1*, *KCNH2*, and *SCN5A* mutations by amino acid coding, frequency, location, and type, please see the online version of this article.

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

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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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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]

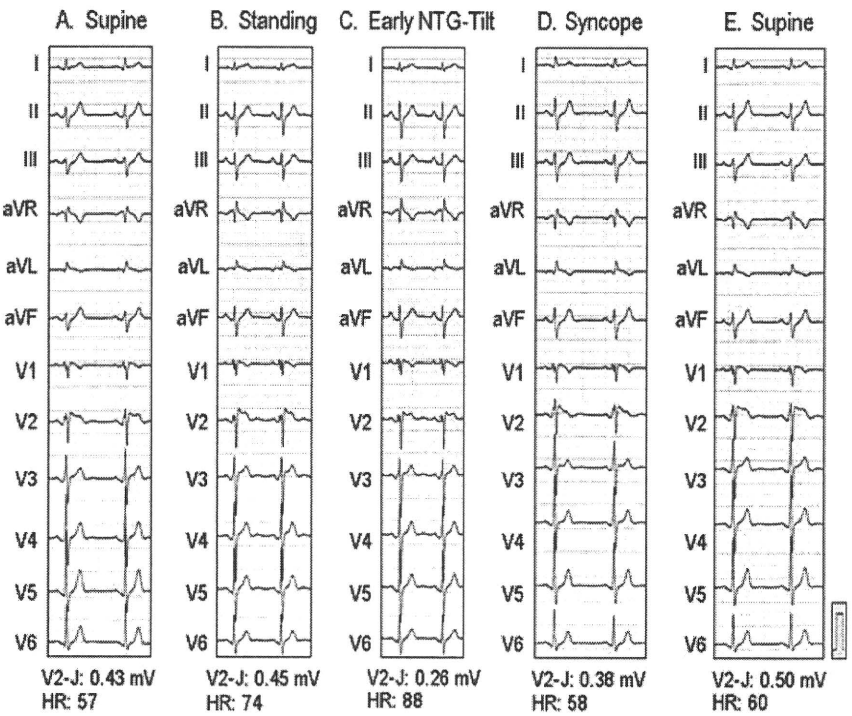

Figure 1. *The12-leads electrocardiogram (ECG) during head-up tilt test in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada ECG at supine position (A), at standing position (B), at early phase of NTG-Tilt (C), at syncope (D), and at supine position following syncope (E).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

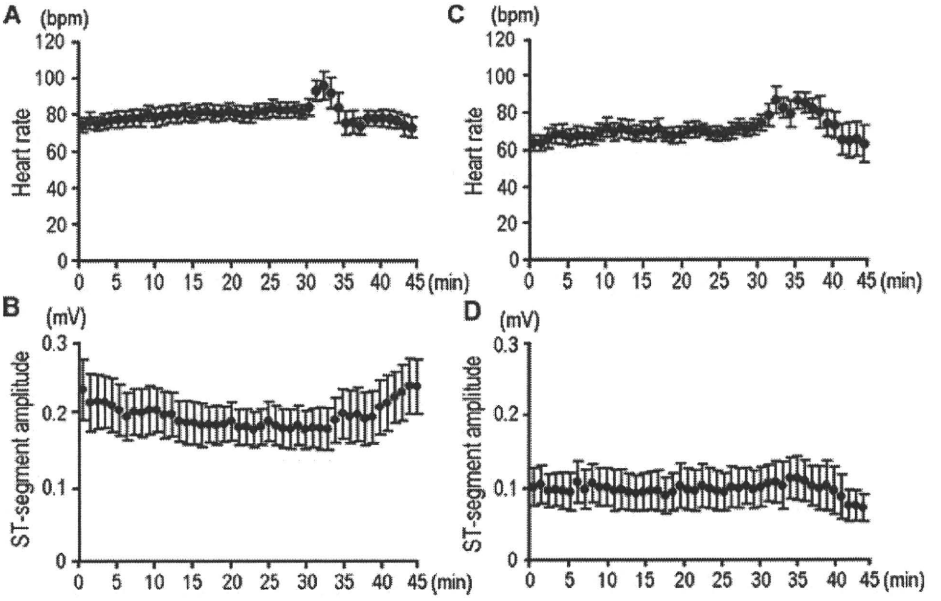

Figure 2. *Response of the heart rate and ST-segment amplitude during the head-up tilt (HUT) test in 16 HUT-positive patients with Brugada electrocardiogram (ECG) (A, B) and in 10 HUT-positive patients with suspected neurally mediated syncope (NMS) (C, D). At first, the passive tilt (Control-Tilt) was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

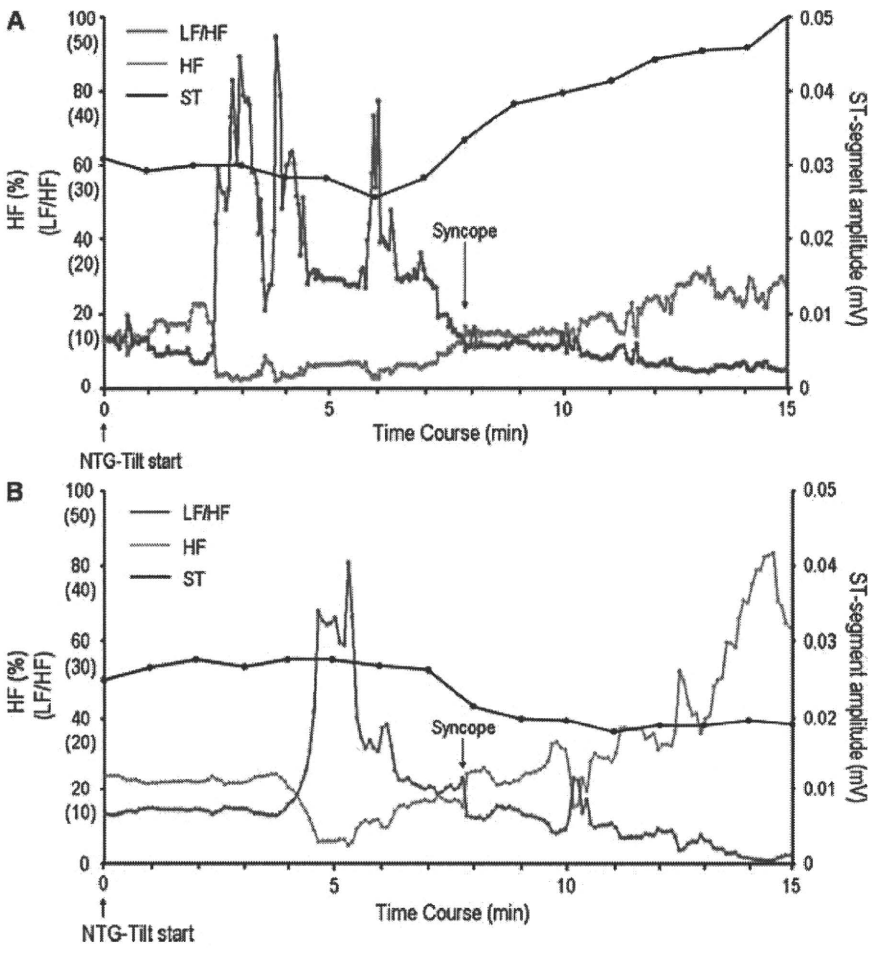

Figure 3. *Autonomic responses during head-up tilt (HUT) test. The autonomic activities in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada electrocardiogram (ECG) (A) and those in a representative NTG-Tilt-positive patient with suspected NMS (B). Before tilt-induced syncope,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

Effects of Combination Therapy With Warfarin and Bucolome for Anticoagulation in Patients With Atrial Fibrillation

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Background: Bucolome, a nonsteroidal antiinflammatory drug, enhances the effects of warfarin. In the present study, the effects of combination therapy (bucolome+warfarin) vs. warfarin alone on atrial fibrillation were investigated.

Methods and Results: Combined therapy resulted in a decrease in the warfarin dose to approximately one-third. The fluctuations of the international normalized ratio and the time in therapeutic range were similar in both groups. There was no adverse effect in either group. Interestingly, uric acid was lower in the bucolome group.

Conclusions: Bucolome enhanced the effects of warfarin, resulting in a decreased dose of warfarin without adverse effects and it showed similar anticoagulant stability to warfarin alone. (*Circ J* 2011; **75:** 201–203)

Key Words: Anticoagulation therapy; Atrial fibrillation; Warfarin

Warfarin is an anticoagulant drug widely used for the prevention of ischemic stroke in patients with atrial fibrillation (AF). However, its anticoagulant effect is influenced by multiple concomitant drug and dietary interactions, making it difficult to maintain therapeutic levels. Warfarin comprises the enantiomers, *S*-warfarin and *R*-warfarin. *S*-warfarin, the more potent, is metabolized predominantly by CYP2C9. Bucolome is a pyrazolidine derivative and has been used as a nonsteroidal antiinflammatory or uricosuric agent. It has been suggested that bucolome enhances the effect of warfarin through inhibition of CYP2C9.[1] Thus, bucolome has sometimes been combined with warfarin to enhance its effects. In Niigata Prefecture especially, the rate of coadministration of warfarin and bucolome is greater than in other regions of Japan. However, the merit or demerit of such combination therapy has not been reported. Therefore, we investigated the effects of bucolome on the stability of the anticoagulation effects of warfarin in patients with AF.

Methods

Study Population

This retrospective case series study consisted of patients with chronic AF who received anticoagulant therapy. Consecutive patients who received a maintenance dose of warfarin in April 2008 were included, but patients who started warfarin within the 2 months before April 2008 were not included. The choice of bucolome+warfarin or warfarin alone was left to the physician's discretion. Patients were excluded if they did not continue to receive warfarin for more than 1 year or if they required temporary interruption of warfarin therapy from any reason, such as an invasive procedure or surgery. Chronic AF was defined as persistent AF of more than 1 year's duration. Major bleeding was defined as reduction of the hemoglobin level of at least 2.0 g/L or requirement of blood transfusion. Stroke was confirmed by computed tomography and/or magnetic resonance scanning.

Statistical Analysis

To study the stability of the international normalized ratio (INR), the coefficient of variation was calculated as follows: coefficient of variation (%)=standard deviation of INR/mean value of INR×100. To calculate the percentage of days when the INR was in the therapeutic range (1.6–2.6), the time in therapeutic range (TTR) was calculated with the method first described by Rosendaal et al.[2] The estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease equation for Japanese patients.[3] Numerical data are presented as mean±SD. Continuous variables were compared with the unpaired t-test and categorical variables were compared with the chi-square test. A P-value less than 0.05 was defined as statistically significant.

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Table 1. Clinical Characteristics of the Study Patients

	Warfarin	Bucolome+ warfarin
n	48	62
Female	22 (45.8%)	18 (29.0%)*
Age, years	69.6±11.7	67.6±10.5
Heart disease		
Valvular heart disease	11 (22.9%)	20 (32.3%)
Prosthetic valve	1 (2.1%)	4 (6.5%)
Ischemic heart disease	8 (16.7%)	7 (11.3%)
Cardiomyopathy	4 (8.3%)	11 (17.7%)
HCM	1 (2.1%)	5 (8.1%)
Comorbidities		
Hypertension	24 (50.0%)	19 (30.6%)*
Diabetes mellitus	9 (18.3%)	24 (38.7%)*
Dyslipedemia	9 (18.3%)	12 (19.4%)
Past major bleeding	6 (12.5%)	3 (4.8%)
Past ischemic stroke	5 (10.4%)	11 (17.7%)
NYHA class		
I	15 (31.3%)	19 (30.6%)
II	29 (60.4%)	41 (66.1%)
III	4 (8.3%)	2 (3.2%)
IV	0	0
Concomitant drugs		
ACEI/ARB	29 (60.4%)	36 (58.1%)
Calcium-channel blocker	15 (31.2%)	21 (33.9%)
β-blocker	29 (60.4%)	36 (58.1%)
Diuretics	27 (56.3%)	40 (64.5%)
Aldosterone antagonist	9 (18.8%)	24 (38.7%)*
Digoxin	23 (47.9%)	34 (54.8%)
Statin	8 (16.7%)	11 (17.7%)
Uricosuric agent	8 (16.7%)	8 (12.9%)
Antiplatelet agent	7 (14.9%)	7 (11.3%)
Laboratory data		
White blood cells, /μl	5,403±1,608	5,715±1,553
Hemoglobin, g/dl	14.0±1.8	13.6±1.9
Platelet, $\times 10^4/\mu l$	17.0±5.2	17.5±5.3
BUN, mg/dl	17.7±5.3	17.8±9.1
Creatinine, mg/dl	0.83±0.22	0.89±0.33
eGFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	65.5±14.6	68.5±22.4
Uric acid, mg/dl	5.7±1.8	4.4±1.6*
AST, IU/L	29.6±11.8	25.8±8.2
ALT, IU/L	23.1±11.6	23.4±10.7
ALP, IU/L	264.1±112.6	242.4±89.8
γ-GTP, IU/L	65.6±75.6	89.3±130.3
BNP, pg/ml	187.8±130.3	186.7±194.2

Data are mean±SD. *P<0.05 vs. Warfarin group.
HCM, hypertrophic cardiomyopathy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; BNP, brain natriuretic peptide.

Table 2. Dose of Warfarin and Stability of INR

	Warfarin	Bucolome+ warfarin
Observation period, months	12.4±0.5	12.7±0.6
Dose, mg	2.96±0.97	1.15±0.48*
INR		
Mean	1.86±0.31	2.04±0.30*
Coefficient variation, %	15.9±8.5	16.3±8.3
TTR (1.6–2.6), %	68.5±27.9	76.1±23.8
Dose adjustment		
N	36 (n=19)	44 (n=26)

Data are mean±SD. *P<0.05 vs. Warfarin group
INR, international normalized ratio; TTR, time in therapeutic range.

Results

Clinical Characteristics (Table 1)

From the hospital database we identified 110 patients with chronic AF who were treated with warfarin, including 62 patients with bucolome (300 mg)+warfarin (bucolome group), and 48 patients with warfarin alone (warfarin alone group). Age, sex, underlying heart disease, and NYHA functional class were not different between the 2 groups. Hypertension and diabetes were more common in the bucolome group than in the warfarin alone group. The frequency of a history of stroke was similar between the 2 groups. There was no difference in concomitant drug use except for aldosterone antagonists. Of the laboratory data, uric acid was lower in the bucolome group than in the warfarin alone group.

Effects of Bucolome

Table 2 shows the dose of warfarin and the stability of the INR during a follow-up of 12.6±0.6 months. In all patients, INR was measured every 1–2 months, and the frequency of INR monitoring during follow-up was similar in both groups (10.1±2.1 times in warfarin alone group, 10.5±2.4 times in bucolome group). The dose of warfarin was lower in the bucolome group (39% of warfarin alone group) compared with the warfarin alone group. Mean INR was higher in the bucolome group than in the warfarin alone group, but in both groups it was within the therapeutic range for Japanese patients with AF.[4] The coefficient of INR variation was also similar between the 2 groups. Furthermore, TTR did not differ between groups. No patient developed stroke during the follow-up period. There was no severe adverse effect related to anticoagulation therapy, such as major bleeding, cytopenia, liver damage or renal impairment, in either group.

Discussion

In the present study, we demonstrated that (1) bucolome reduced the dose of warfarin required to achieve optimal INR levels; and (2) bucolome did not affect INR fluctuation nor did it cause any adverse effects.

Bucolome enhances the anticoagulant effect of warfarin, and is sometimes coadministered with warfarin for prevention of ischemic stroke in AF patients in Japan.[1,5–7] In our study, bucolome reduced the dose of warfarin by 61%, similar to prior studies (58–60% decrease).[1,6] We also found that bucolome did not affect the stability of the anticoagulant effects of warfarin. However, when bucolome is coadministered with warfarin, warfarin has to be in the powdered form, which in this study was administered in all patients in bucolome group, but did not result in increased INR fluctuation. Bucolome did not affect the frequency of stroke or major bleeding, but long-term follow-up may be needed to clarify this issue.

Because bucolome is a nonsteroidal antiinflammatory agent, adverse effects such as renal impairment and gastroin-

testinal bleeding, might be caused by 1 year's administration. However, coadministration of bucolome with warfarin did not cause any adverse effects. Interestingly, bucolome reduced the uric acid levels. Recent studies have shown that uric acid is a marker of inflammation and oxidative stress, both of which are important pathophysiological features of AF.[8–10] Furthermore, increased levels of uric acid were associated with chronic AF in a recent study.[11] Thus, bucolome may have additional beneficial effects, at least for patients with paroxysmal AF.

This study has some limitations. It was a small, retrospective study conducted in a single institution, and further prospective studies are necessary to generalize our results and to investigate adverse effects of the combination of warfarin and bucolome.

In conclusion, bucolome enhanced the effects of warfarin, resulting in a decrease of the warfarin dose without any adverse effects and showed similar anticoagulant stability to warfarin alone.

Disclosures

None declared.

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CASE REPORT

Suppression of Storms of Ventricular Tachycardia by Epicardial Ablation of Isolated Delayed Potential in Noncompaction Cardiomyopathy

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A 65-year-old recipient of an implantable cardioverter defibrillator suffering from ventricular noncompaction developed storms of ventricular tachycardia (VT). Epicardial voltage mapping revealed the presence of a large low-voltage area in the left ventricular apical and inferoposterior wall, and isolated delayed potential was recorded over 1.5 cm in the posterior border between low and normal myocardial voltage. Pacemapping at the delayed potential recording site produced two different QRS depending on pacing output strength, and these two QRS morphologies were similar to clinically documented VTs. During one of the VTs, a mid-diastolic potential was recorded from the site with the delayed potential, and rapid pacing produced concealed entrainment. After epicardial radiofrequency ablation of the isolated delayed potential, VTs were noninducible and the VT storm was suppressed. (PACE 2010; 1–5)

ventricular noncompaction, ventricular tachycardia, electrical storm, epicardial catheter ablation

Introduction

Ventricular noncompaction (VNC) is a cardiomyopathy characterized by the formation of deep intertrabecular recesses substituting for compact endocardium and a thin compact epicardial layer.[1–3] Congestive heart failure, embolic events, and ventricular arrhythmias are major complications of VNC.[1–3] We recently observed a patient who presented with VNC complicated by storms of ventricular tachycardia (VT). During electroanatomical mapping with a CARTO® Navigation System (BiosenseWebster, Diamond Bar, CA, USA), a wide low-voltage area was found on the left ventricular (LV) compact epicardial, but not noncompact endocardial, area. Epicardial radiofrequency (RF) catheter ablation targeted at the isolated delayed potential in the low-voltage area suppressed the VT storms.

Case Report

A 65-year-old man was readmitted to our hospital for treatment of VT1 storms. He had been hospitalized initially 6 weeks earlier for the treatment of VT1 (Fig. 1A). The standard, 12-lead electrocardiogram (ECG) showed sinus rhythm with incomplete right bundle branch block and low limb leads voltage (Fig. 1D). Two-dimensional echocardiography showed diffuse hypokinetic LV wall motion and the presence of deep intertrabecular recesses, particularly prominent in the LV apical and inferolateral regions. Using cardiac magnetic resonance, Petersen et al. reported that pathological trabeculation could be distinguished by determining the ratio of noncompacted to compacted myocardium of >2.3 in diastole.[3] In this patient, cardiac magnetic resonance imaging showed diastolic myocardial noncompaction/compaction dimensions of 16/5 mm (ratio = 3.2) in the LV apical segment, and this was compatible with the diagnosis criterion of VNC.

The patient underwent cardiac catheterization and angiograms, which revealed the presence of normal intracardiac pressures and coronary vessels, and diffuse LV hypokinesis (left ventricular ejection fraction = 29%). During the electrophysiologic study in the absence of any antiarrhythmic drugs, endocardial electroanatomical mapping showed electrograms <1.5 mV in amplitude in a small area of the LV inferior wall, contrasting with the >2.0 mV endocardial signals recorded in the other LV regions (Fig. 2A). Programmed electrical stimulation reproducibly induced VT2, which had not been observed clinically (Fig. 1B). The earliest

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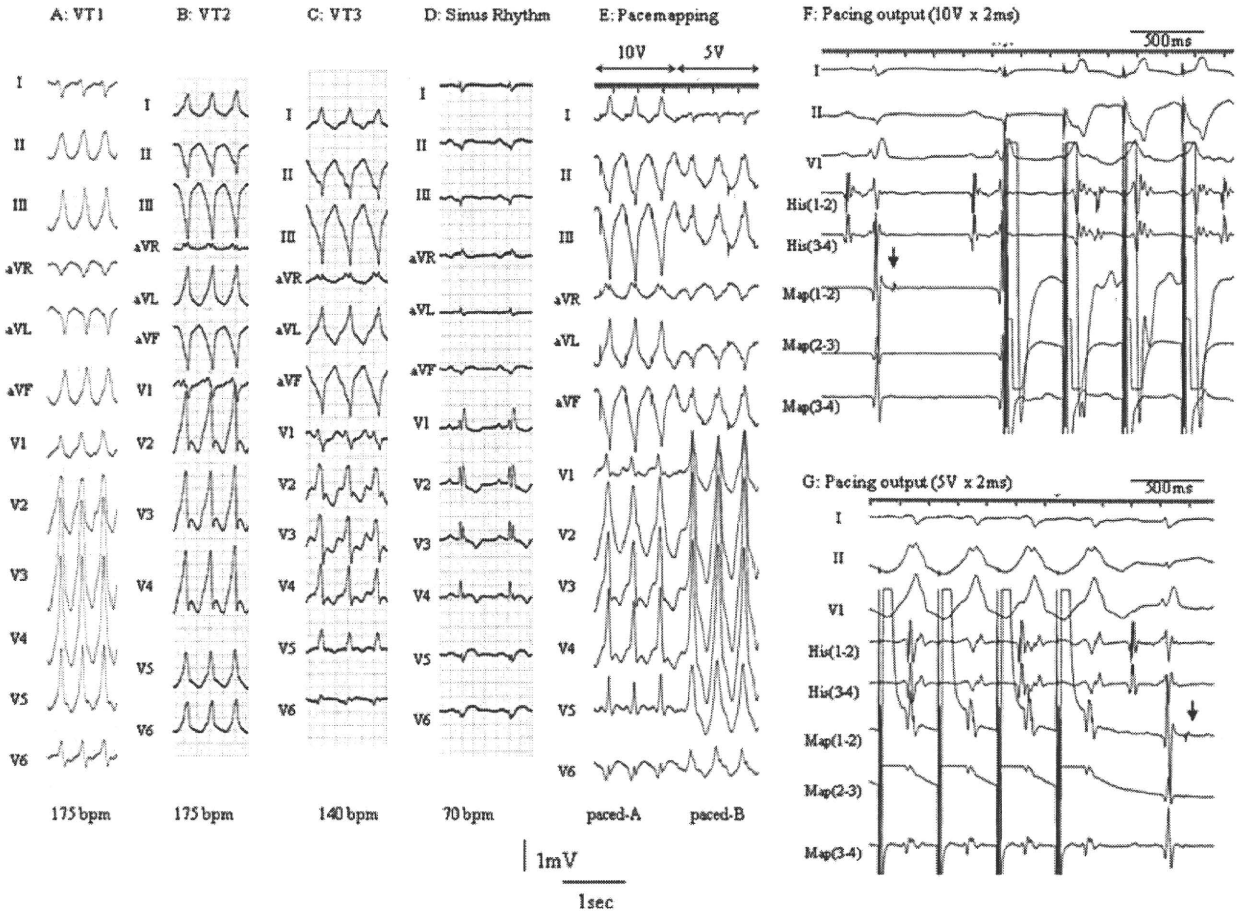

Figure 1. *Surface 12-lead electrocardiograms (A–E) and electrophysiologic study (F and G). (A) Spontaneous VT1. (B) VT2 was induced during the first electrophysiologic study. (C) VT3 was reproducibly induced during the second study. (D) Baseline electrocardiogram. (E) Pacemapping at the site with the isolated delayed potential showed two paced QRS morphologies depending on the pacing output. (F) Pacemapping at a 10 V/2-ms output produced paced QRS-A with a short ST-QRS interval. (G) Pacemapping from the same site at a 5 V/2-ms output produced paced QRS-B with a 120-ms stimulus to QRS interval. His = distal (1–2) and proximal (3–4) bipolar recordings from the quadripolar catheter placed in the His bundle region. Map = distal (1–2), intermediate (2–3), and proximal (3–4) bipolar recordings from the mapping catheter.*

site of endocardial activation of VT2 was located in the LV inferobasal area (Fig. 2B), though its onset was nearly coincidental with the onset of the QRS complex. Using a 4-mm-tip standard ablation catheter, RF energy (55°C, 40–50 W) was unsuccessfully delivered three times to that site. The patient received a Virtuoso® DR dual-chamber implantable cardioverter defibrillator (ICD) (Medtronic Inc., Minneapolis, MN, USA) and was placed on a regimen of sotalol 240 mg daily. He remained clinically stable until his rehospitalization for management of electrical storms due to VT3 (Fig. 1C).

Since the VT3 storms were refractory to antiarrhythmic drugs, we proceeded with mapping of the epicardium and inserted the electrode catheter percutaneously into the pericardial space. At the time of study, VT3 was the only reproducibly induced VT on the treatment of sotalol (240 mg daily). Electroanatomical mapping revealed the presence of a wide apical and inferoposterior LV myocardial region with electrograms <1.5 mV in amplitude (Fig. 2C). Near the posterior border, between the normal and low-voltage areas, an isolated delayed potential was recorded over a 1.5-cm-long segment during sinus rhythm (Figs. 1F and G and 2C). Pacing in the segment at an output of 10 V/2 ms captured the isolated delayed potential, along with the surrounding myocardial region, resulting in paced QRS-A preceded by

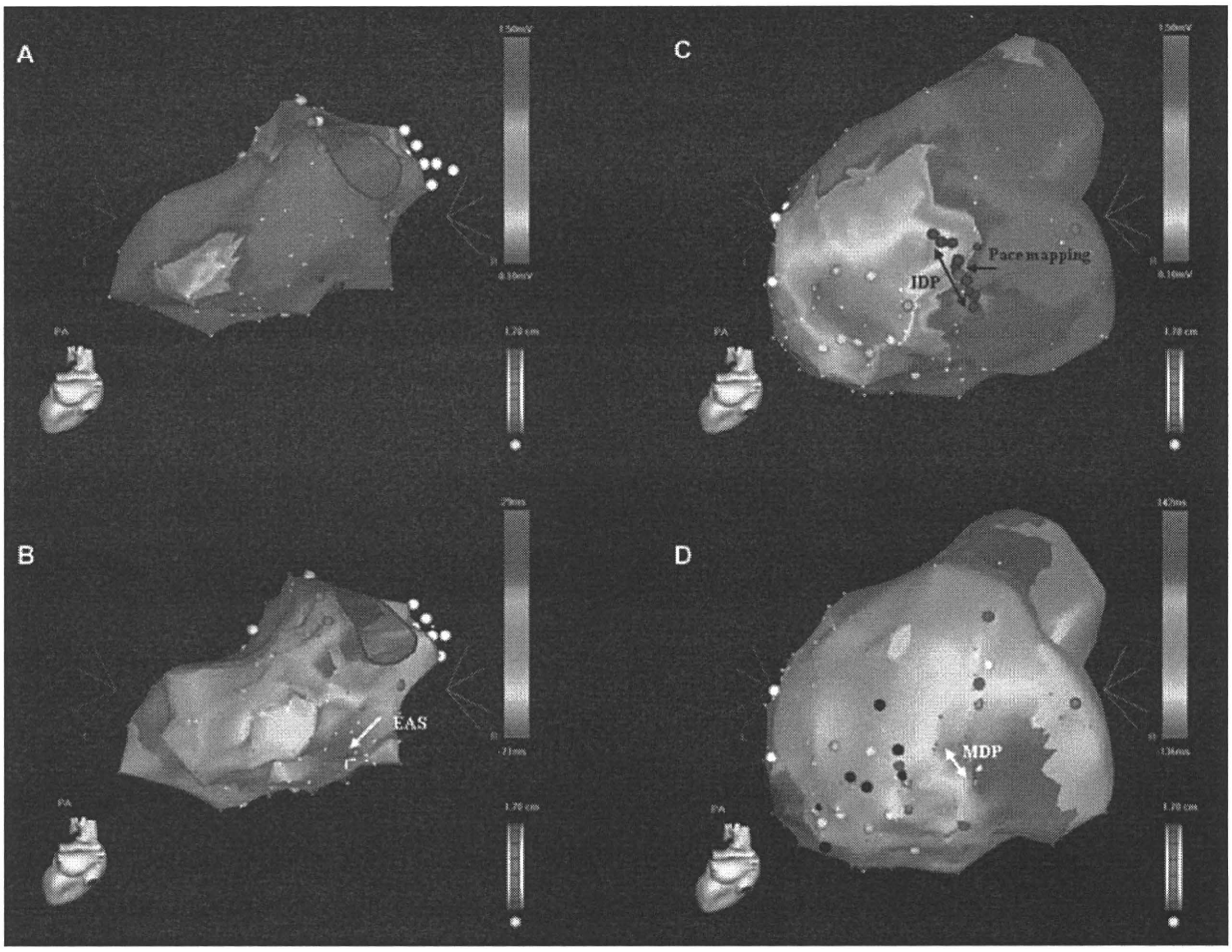

Figure 2. *Electroanatomical mapping. Left ventricular posterior views of endocardial (A and B) and epicardial mapping (C and D). Voltage mapping during sinus rhythm (A and C) and activation mapping during VT2 (B) and VT3 (D) were shown. A black-bidirectional arrow (C) shows the segment where the isolated delayed potential (IDP) was recorded. The earliest endocardial activation site (EAS) during VT2 (B, marked by a white arrow) was almost in opposite the area where isolated delayed potential was recorded during sinus rhythm. A white-bidirectional arrow (D) indicates the site showing mid-diastolic potential during VT3, but the activation sequence of the map (D) did not cover the VT3 cycle length. A black arrow (C) shows the site induced two paced QRS morphologies, and brown tags (A and C) indicate ablation points.*

a short stimulus (St) to QRS (St-QRS) interval (Fig. 1E and F), similar to VT3 (Fig. 1C). Pacing at the same site at an output of 5 V/2 ms occasionally captured the isolated delayed potential alone. The paced QRS (QRS-B) was preceded by a 120-ms St-QRS interval (Fig. 1E and G). Although the paced QRS-B was unlike any of the recorded VTs, it was closest to VT1. During VT3, at the central segment with the isolated delayed potential, a low-amplitude, mid-diastolic potential was recorded 215 ms prior to the QRS onset, and a broad, high-amplitude potential 15 ms before the onset of the QRS complex (Figs. 2D and 3A). Entrainment pacing, which occasionally captured the mid-diastolic potential, showed concealed fusion on the surface ECG, and associated with a postpacing interval and cycle length of VT3, both measuring 430 ms. Furthermore, the 215-ms interval between the mid-diastolic potential and onset of the QRS complex during VT3 was identical to the interval between the stimulus artifact and the onset of the next QRS complex (Fig. 3A). On the other hand, entrainment pacing with capture of the high-amplitude local potential was associated with subtle fusion on the surface ECG and a 450-ms postpacing interval, slightly longer than the 430-ms VT3 cycle length (Fig. 3B). Pacing site, stimulus output, and initial coupling interval

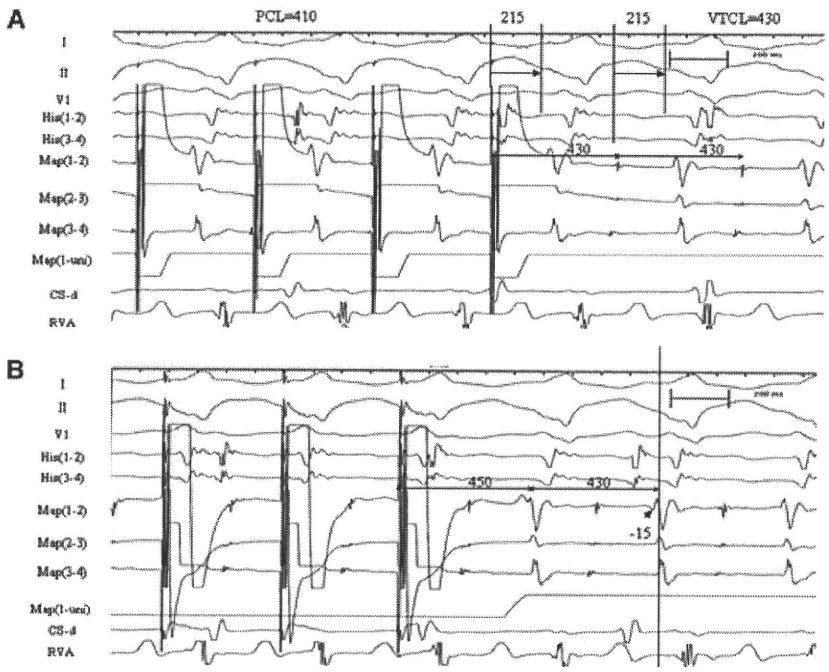

Figure 3. *Entrainment mapping. During VT3, pacing with capture of the mid-diastolic potential was associated with concealed entrainment (A), whereas pacing with capture of the high-amplitude potential was associated with subtle fusion on the surface ECG (B). See text for more detailed discussion. PCL = pacing cycle length; VTCL = ventricular tachycardia cycle length; CS-d = distal coronary sinus; RVA = right ventricular apex; Map (1-uni) = distal unipolar electrogram from the mapping catheter; other abbreviations as in figure 1.*

were not different between the two-entrainment phenomenons. Unstable positioning of the mapping catheter during the epicardial pacing for VT3 might be a reason whether the pacing captured either the mid-diastolic potential or large potential. On electroanatomical mapping, the segment showing the isolated delayed potential was located on the epicardial surface opposite the earliest endocardial activation site during VT2 (Fig. 2B and C). Since VT3 was hemodynamically unstable, we delivered linear RF, using a 4-mm-tip, open irrigation catheter (30 mL/min, 25–35 W, temperature limit 40°C) to the segment where the isolated delayed potential was recorded. The amplitude of the delayed potential decreased with each delivery of RF energy, until its complete elimination after 13 RF applications. VT was no longer inducible immediately and 2 weeks after RF ablation, and no VT has not been recurred with the treatment of sotalol 80 mg daily up to now.

Discussion

The electrophysiological mechanism of VT and characteristics of the arrhythmogenic substrate in patients presenting with VNC remain unclear.[1,2] One may reasonably hypothesize that the arrhythmogenic substrate of VNC is in the subendocardium, since decreased myocardial perfusion, increased subendocardial fibrosis, or both have been observed in the zone of myocardial noncompaction.[4,5] However, the site of VT origin in VNC was determined at various sites in each case report.[6–8] In our patient, the arrhythmogenic substrate was considered to be located either in the compact epicardial or noncompact myocardium just beneath the epicardium instead of the noncompact endocardial LV area, and epicardial RF delivery effectively eliminated the VT storms. Therefore, we believe that epicardial mapping should be performed when the site of VT origin has not been found by endocardial mapping in patients suffering from VNC.

During the epicardial mapping, we detected isolated delayed potential in the border segment between normal and low-voltage myocardium in the LV posterior wall (Figs. 1F and G and 2C). We considered that the isolated delayed potential was associated with a critical area of the VT3 circuit because, during the VT3, mid-diastolic potential was recorded in the segment and its capture caused transient concealed entrainment. Since the

interval between the mid-diastolic potential and the onset of the QRS complex represented 50% of the VT3 cycle length (215/430 ms), it marked the center of the slow pathway of the reentry circuit. Interestingly, pacemapping from the site of isolated delayed potential induced paced QRS-A or QRS-B, depending on the pacing output. Paced QRS-B was associated with a long St-QRS interval and a morphology similar to VT1, whereas paced QRS-A resembled the QRS of VT3. These findings might suggest that the VT3 and VT1 originated from the same arrhythmogenic area. The origin of VT2 might also have been located near that site, as the earliest endocardial activation during VT2 was mapped in an area opposite the epicardial segment of isolated delayed potential recording during sinus rhythm. VT was no longer inducible after epicardial ablation. However, the arrhythmogenic substrate was a potential source of multiple slow pathways and pleomorphic VT. Therefore, we will follow this patient in our ambulatory department with a view to detect possible recurrences of VT, progression of cardiac dysfunction due to VNC, or both.

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