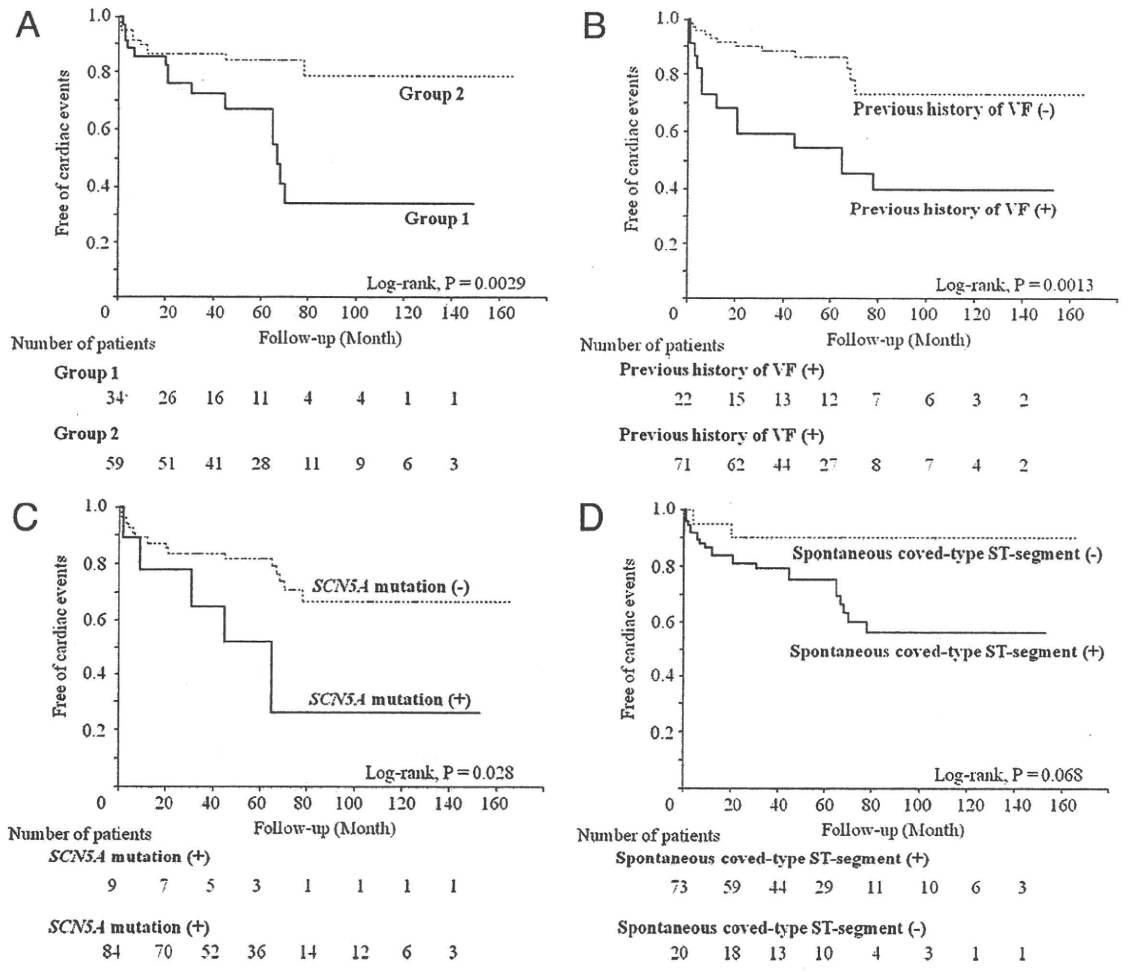

Figure 4 **Kaplan-Meier Analysis of Cardiac Events During Follow-Up**

Kaplan-Meier analysis of **(A)** cardiac events during follow-up, depending on patterns in response to ST-segment elevation during exercise test (groups 1 and 2), **(B)** incidence of previous episode of ventricular fibrillation (VF), **(C)** *SCN5A* mutation, and **(D)** spontaneous coved-type ST-segment elevation. Group 1 Brugada patients had a significantly higher cardiac event rate than did group 2 Brugada patients (log-rank, p = 0.0029). Brugada patients with previous episodes of VF or with *SCN5A* mutation had significantly greater values for occurrence of subsequent cardiac events than did patients without VF episodes or *SCN5A* mutation (p = 0.0013, p = 0.028, respectively), whereas spontaneous coved-type ST-segment elevation in Brugada patients did not predict cardiac events compared with patients not having such ST-segment elevation (p = 0.068).

Further study with a larger number of BrS patients will be required to evaluate the significance of the index as a predictor of subsequent cardiac events.

As for BrS patients with only syncope, subsequent cardiac events occurred in 50% (6 of 12) patients who exhibited ST-segment augmentation at early recovery. Asymptomatic

Table 3 **Predictive Capabilities of Cardiac Events**

		Univariate Analysis		Multivariate Analysis	
	Positive, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
Previous episodes of VF	22 (24%)	3.40 (1.54–7.53)	0.003	3.25 (1.43–7.37)	0.005
Augmentation of ST-segment elevation at early recovery phase	34 (37%)	3.17 (1.42–7.09)	0.005	3.17 (1.37–7.33)	0.007
SCN5A mutation	9 (10%)	2.86 (1.07–7.66)	0.037		
Spontaneous coved-type ST-segment	72 (77%)	3.51 (0.83–14.9)	0.089		
Late potential	58/91 (64%)	2.25 (0.84–5.99)	0.11		
VF inducible in EPS	59/78 (76%)	0.73 (0.30–1.75)	0.48		
Family history of SCD or BrS	23 (25%)	1.19 (0.47–3.02)	0.72		

BrS = Brugada syndrome; CI = confidence interval; EPS = electrophysiologic study; HR = hazard ratio; other abbreviations as in Table 2.

Table 4 **Incidence of Cardiac Events According to Symptoms Before Exercise Testing**

Type	n	Treadmill Exercise Test	n	VF Occurrence	p Value (vs. Group 1)
Documented VF	22	Group 1	7	6 (86%)	
		Group 2	15	7 (47%)	0.14
Syncope alone	35	Group 1	12	6 (50%)	
		Group 2	23	3 (13%)	0.016
Asymptomatic	36	Group 1	15	3 (20%)	
		Group 2	21	0 (0%)	0.039

The p value was calculated according to the log-rank test.
VF = ventricular fibrillation.

patients who had ST-segment augmentation at early recovery had a higher incidence of cardiac events than patients who did not. These data suggested the potential utility of exercise testing to predict cardiac events for patients with BrS who have had previous episodes of only syncope but not VF or who have had no symptoms.

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Key Words: Brugada syndrome ■ exercise testing ■ ST-segment elevation.

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Heart rate-dependent variability of cardiac events in type 2 congenital long-QT syndrome

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Aims We aimed to examine the validity of heart rate (HR) at rest before β-blocker therapy as a risk factor influencing cardiac events (ventricular fibrillation, torsades de pointes, or syncope) in long QT type 2 (LQT2) patients.

Methods and results In 110 genetically confirmed LQT2 patients (45 probands), we examined the significance of variables [HR at rest, corrected QT (QTc), female gender, age of the first cardiac event, mutation site] as a risk factor for cardiac events. We also evaluated frequency of cardiac events in four groups classified by the combination of basal HR and QTc with cutoff values of 60 b.p.m. and 500 ms to estimate if these two electrocardiographic parameters in combination could be a good predictor of outcome (mean follow-up period: 50 ± 39 months). Logistic regression analysis revealed three predictors: HR <60 b.p.m., QTc ≥500 ms, and female gender. When the study population was divided into four groups using the cutoff values of 60 b.p.m. for HR and 500 ms for QTc, the cumulative event-free survival by the Kaplan–Meier method was significantly higher in the group with HR ≥60 b.p.m. and QTc <500 ms than in the group with HR <60 b.p.m. and QTc <500 ms or that with HR <60 b.p.m. and QTc ≥500 m ($P < 0.05$). Irrespective of QTc interval, LQT2 patients with basal HR <60 b.p.m. were at significantly higher risk.

Conclusion The basal HR of <60 b.p.m. is a notable risk factor for the prediction of life-threatening arrhythmias in LQT2 patients.

Keywords Long QT syndrome • Arrhythmia • Genetics • Heart rate • Torsades de pointes

Introduction

Long QT syndrome (LQTS) is a primary electrical disease characterized by an abnormality in myocardial repolarization that leads to the prolongation of QT interval, morphological changes in T waves, and torsades de pointes (TdP) type of ventricular tachyarrhythmias on surface electrocardiogram (ECG).[1] Studies on genotype–phenotype correlation identified the clinical characteristics in each genetic subgroup, which made it possible to diagnose and introduce β-blocker therapy (BBT) appropriately in LQTS patients.[2–4] In patients with LQTS type 1 (LQT1), β-blockers are quite effective, whereas they are less effective in suppressing arrhythmic events in LQT2 and 3.[2]

Previous studies have demonstrated the importance of evaluating patients by clinical symptoms, gender, causative mutations, the type or biophysical function of mutations, and corrected QT (QTc) interval to stratify the arrhythmic risk in LQTS.[3,5–14] Heart rate (HR) has been recognized since the establishment of LQTS as a clinical entity, and a low HR for age was included in the diagnostic criteria.[15] A recent study by Schwartz *et al.*[16] demonstrated that a lower resting HR and a relatively low baroreflex sensitivity in *KCNQ1* A341V carriers are protective factors,

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whereas HR at rest in other subtypes of LQTS has not been fully investigated. In clinical practice, we have noted that in some cases of LQT2 that TdP was triggered by HR of <60 b.p.m. and suppressed by pacing at 80 b.p.m., which made us evaluate the importance of HR in arrhythmic events of LQT2 patients. For these reasons, we aimed to analyse whether HR at rest before BBT could be a novel risk factor for cardiac events besides gender, genetic locus, and prolonged QT interval in LQT2. We also evaluated the relationship between HR at rest and arrhythmic events before and after BBT through the analysis of clinical data on patients with LQT2.

Methods

Study population

From September 1996 to July 2009, 587 probands with QT prolongation underwent genetic testing in three institutes in Japan, Shiga University of Medical Science, Kyoto University Graduate School of Medicine, and the National Cardiovascular Center. One hundred and fifty-two probands (26%) were genotyped as LQT2. We also screened mutations in *KCNQ1*, *SCN5A*, *KCNE1–3*, and *KCNJ2* using the standard genetic tests[17–20] and excluded 20 probands with compound mutations and/or modifier single-nucleotide polymorphisms known to affect the QT interval (*KCNH2* K897T and *KCNE1* D85N).[21,22] The remaining 132 probands were found to have a single *KCNH2* mutation, and among them, we excluded from analyses patients under 15 years and those without detailed clinical information or with medication (except for β-blocker) which could influence baseline ECG measurements at the first medical contact and thereafter. Children <15 years old were not studied because they had relatively high basal HR. Family members of the 152 probands were recruited for the analysis if we could obtain necessary clinical information and if they were over 15 years old. As a result, the study population became 110 patients (45 probands and 65 family members) from 74 unrelated Japanese LQT2 families.

Both symptomatic and asymptomatic patients were included in the groups of probands and family members. Regardless of being probands or family members, patients were defined as symptomatic when they had a history of cardiac events (defined as ventricular fibrillation, TdP, or syncope due to ventricular arrhythmia) at the first medical contact or at the time of yearly follow-up. Patients with an apparent history of vasovagal syncope were not included in the study. The protocol for genetic analysis complied with the Declaration of Helsinki and was approved by the institutional ethics committees and performed under their guidelines. All individuals or their guardians gave written informed consent to genetic and clinical data analyses. Follow-up data were obtained from patients' regular hospitals working with the authors in case patients lived far from our institutions or hospitals and were not able to visit us.

Genetic analysis and characterization

Genomic DNA was isolated from venous blood lymphocytes using the QIAamp DNA blood midikit (Qiagen, Hilden, Germany). Established primer settings were used to amplify the entire coding regions of known LQTS genes from genomic DNA.[17–20] Denaturing high performance liquid chromatography (DHPLC) or direct sequencing techniques were employed as described elsewhere.[11] Polymerase chain reaction fragments presenting abnormal signals in DHPLC analysis were subsequently sequenced by the dideoxynucleotide chain termination method with fluorescent dideoxynucleotides on an ABI 3113xl genetic analyzer (PE Applied Biosystems).

The pore region of the *KCNH2* channel was defined as the area extending from S5 to the mid-portion of S6 involving amino acid residues from 550 through 650 according to the previous report.[10] The non-pore region included the N-terminus region, transmembrane domains apart from the pore region and the C-terminus region.

Clinical characterization

Routine demographic data and basal 12-lead ECGs were obtained from all subjects at the first medical contact as well as at yearly follow-up. In 104 patients, ECG parameters were measured before BBT was introduced. The remaining six patients, in whom BBT was started after the first cardiac event by an attending physician in other hospitals, visited a university hospital for further diagnostic confirmation of the symptoms. One of the six patients experienced aborted sudden cardiac death, four had documented TdP, and one had a syncopal attack. After obtaining informed consent, BBT was discontinued for more than five times the half life and examinations were performed, including a blood test, basal ECG, chest X ray, echocardiogram, and treadmill test for the diagnosis of congenital long QT syndrome.

Electrocardiograph parameters measured in the study were HR and QT interval. Rate-dependent QT intervals were corrected for HR using Bazett's method. QT interval was manually measured in lead V_5 using the tangent method[4] with an average of 2 or 3 consecutive beats by three investigators who were completely unaware of the patients' clinical and genetic state. There were no significant differences in the measured data among three investigators. Bifid T waves, but not U waves, were included in the QT measurements. In the presence of bifid T waves, the end of the second T wave was defined as the end of the QT interval. If ECG recordings were obtained during a cardiac event, such as the appearance of frequent ventricular tachycardia, TdP, or cardiac arrest, they were requested to perform another examination after patient's general status had improved.

Data on patients who received BBT after the initial check-up were evaluated, including the dose of each drug, HR under medication, and recurrent arrhythmic episodes. Other treatments, such as implantable cardioverter-defibrillator (ICD) implantation and surgical left cardiac sympathetic denervation, were also evaluated. Follow-up data, including the occurrence of cardiac events and therapeutic changes, were collected retrospectively.

Statistical analysis

Student's *t*-test was employed to compare continuous data. Differences in frequencies were analysed by the χ^2 test or Fisher's exact test. Analysis of variance was used to test differences of variables among more than three groups. Stepwise regression analysis was performed to determine predictors of cardiac events. Variables with $P < 0.05$ on univariate analysis were included in a logistic regression model with cardiac events as dependent variables. To determine the connection of the selected clinical variables with the occurrence of cardiac events, odds ratios for unadjusted data and their 95% confidence intervals were calculated. The cumulative probability of the first cardiac event between 15 and 50 years old was estimated using the Kaplan–Meier method. The Cox proportional-hazards survivorship model was used to investigate whether there were any prognostic factors that could influence the occurrence of cardiac events. Data are reported as the mean ± SD. Two-sided probability values <0.05 were considered significant. Statistical calculations were performed using SPSS software (version 18.0J).

Results

Clinical and genetic characteristics

The study population consisted of 110 consecutive patients from 74 unrelated Japanese LQT2 families (*Table 1*). The baseline ECG showed that the mean HR of probands tended to be lower than that of family members ($P = 0.06$).

All patients were genotyped to be a heterozygous carrier of 70 different *KCNH2* mutations (18 in the N-terminus, 15 in non-pore regions, 13 in pore regions, and 24 in the C-terminus). Forty-three mutations were missense mutations, 15 were deletion/insertions, 9 were frameshifts, and 3 were nonsense mutations.

Table 1 Basal characteristics of the study population

	All ($n = 110$)	Proband ($n = 45$)	Family member ($n = 65$)
Clinical characteristics			
Age (years)	40.8 ± 17.5 (15–87)	31.2 ± 15.6 (15–77)	47.4 ± 15.6 (16–87)**
Sex (male/female)	40/70	10/35	30/35*
Symptomatic patients [*n* (%)]	48 (44)	38 (84)	10 (15)**
Cardiac arrest (*n*)	7	4	3
Syncope (*n*)	46	38	8
Both (*n*)	5	4	1
ECG			
HR (b.p.m.)	62 ± 10	60 ± 9	63 ± 11
QTc (ms)	483 ± 58	508 ± 60	467 ± 50**

*$P < 0.05$ vs. proband.
**$P < 0.001$ vs. proband.

Factors determining cardiac events in LQT2 patients

We first evaluated whether HR and other variables (age at onset of cardiac events, female gender, site of mutation, missense mutation, and QTc) served as risk factors for cardiac events in LQT2 patients. Univariate analysis (*Table 2*) showed that HR of <60 b.p.m. *per se* was a significant risk for cardiac events ($P < 0.01$). In addition, female gender, HR as a continuous variable, a QTc interval of ≥500 ms, and pore site mutation were associated with an increased risk for cardiac events ($P < 0.05$). Other variables such as age at onset of cardiac events, sites of mutation (non-pore transmembrane, N-terminal, and C-terminal), and missense mutation were not statistically significant.

Multivariate analysis (*Table 2*) was subsequently performed using female gender, HR of <60 b.p.m., QTc of ≥500 ms, and pore site mutation. As for HR, we chose HR of <60 b.p.m. for multivariate analysis because we aimed to clarify if low HR of <60 b.p.m. was a significant risk factor for cardiac events. As shown in *Table 2*, female gender, HR <60 b.p.m., and QTc ≥500 ms were revealed to be significant risk factors for cardiac events ($P < 0.05$).

Bradycardia as an arrhythmic risk factor in LQT2 patients

We employed two ECG parameters, HR and QTc, to scrutinize who were more prone to have cardiac events in our LQT2 cohort. Using cutoff values of 60 b.p.m. for HR without β-blockers and 500 ms for QTc, we classified 110 LQT2 patients into four groups (*Figure 1*). Closed and open circles in the figure indicate symptomatic and asymptomatic patients, respectively (including both probands and family members). There were only eight symptomatic patients (23%) in the quadrant area of HR ≥60 b.p.m. and QTc <500 ms. In contrast, in the quadrant area defined as HR <60 b.p.m. and QTc ≥500 ms, 12 subjects (86%) experienced cardiac events ($P < 0.05$, vs. HR ≥60 b.p.m. and QTc <500 ms).

Table 2 Predictors of cardiac events (syncope, aborted cardiac arrest, or sudden cardiac death) in univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age at onset	1.08 (0.78–1.49)	0.639		
Female gender	3.56 (1.51–8.38)	0.004	4.54 (1.72–12.00)	0.002
HR <60 b.p.m.	2.83 (1.30–6.16)	0.009	4.46 (1.77–11.24)	0.001
HR (continuous variable)	0.95 (0.91–0.99)	0.022		
QTc ≥500 ms	2.65 (1.18–6.00)	0.019	2.93 (1.13–7.59)	0.026
Mutation location				
Pore	2.45 (1.07–5.60)	0.034	1.77 (0.70–4.48)	0.230
Transmembrane, non-pore	0.91 (0.27–3.08)	0.914		
N-terminal	0.83 (0.33–2.04)	0.677		
C-terminal	0.57 (0.26–1.27)	0.169		
Missense mutation	2.10 (0.91–4.85)	0.081		

Table 3 summarizes the baseline characteristics of four groups divided by HR and QTc. The group of HR ≥60 b.p.m. and QTc <500 ms was defined as Group A, the group of HR <60 b.p.m. and QTc <500 ms as Group B, HR ≥60 b.p.m. and QTc ≥500 ms as Group C, and HR <60 b.p.m. and QTc ≥500 ms as Group D. There were no significant differences among four groups regarding age at baseline ECG recording, age at the first event, percentages of female gender, and BBT. In Group A, the number of proband was significantly lower than that in Groups B and D. The incidence of syncope or aborted cardiac arrest in Group A was significantly lower than in the Groups B and C. In groups of HR <60 b.p.m. (B and D), patients with QTc ≥500 ms (Group D) had more arrhythmic events than those with QTc <500 ms (Group B).

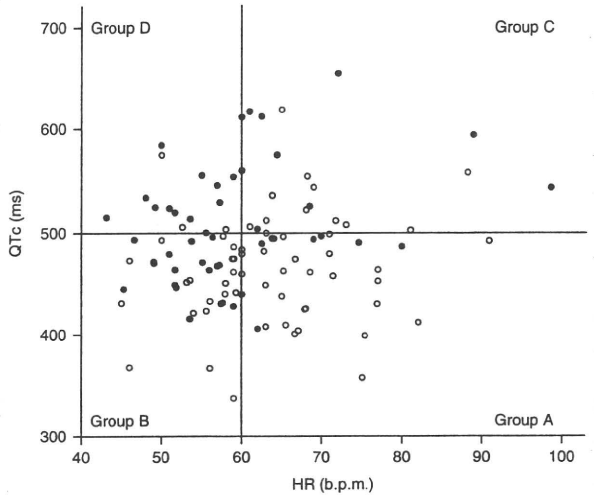

Figure 1 Distribution of KCNH2 mutation carriers according to the resting HR and QTc duration. Closed and open circles indicate symptomatic and asymptomatic patients, respectively. Two solid lines in the graph are drawn using the cutoff values of 60 b.p.m. and 500 ms. QTc was measured in lead V5. Groups A-D in the graph correspond to those in the text, *Table 3* and *Figure 2*.

We then estimated the cumulative probability of the first cardiac event between the age of 15 and 50 in four groups (Groups A–D, *Figure 2*). The Kaplan–Meier analysis of all subjects (*Figure 2A*) showed that cumulative event-free survival was significantly different ($P = 0.007$ by the log-rank test) and when adjusted for multiple comparisons, cumulative event-free survival was higher in Group A than in groups of HR <60 b.p.m. ($P = 0.014$ vs. Group B, $P = 0.001$ vs. Group D). In contrast, the survival rate was not statistically different among Groups B–D.

In *Figure 2B* and *C*, we examined the clinical course of 45 probands and 65 family members separately. The Kaplan–Meier analysis revealed no statistical difference in probands (*Figure 2B*, $P = 0.206$ by the log-rank test), whereas in family members, cumulative event-free survival was significantly different among the subgroups (*Figure 2C*, $P = 0.017$ by the log-rank test, $P = 0.058$ for Group A vs. Group B, $P = 0.002$ for Group A vs. Group D in multiple comparisons). Thus, the statistical difference in overall subjects may result from the prognosis of family members in our study population.

Finally, in order to assess the significance and independence of HR and QTc for cardiac events, we evaluated the parameters with the Cox proportional-hazards survival model (*Table 4*). The values of HR and QTc were centred at 60 b.p.m. and 500 ms for ease of interpretation. Compared with patients in Group A, patients in groups of HR <60 b.p.m. (Groups B and D) showed a higher risk for cardiac events by 2.6–4.4-fold. Although the hazard ratio in Group C was 2.16, there was no statistical difference between Groups A and C.

Table 3 Baseline clinical characteristics of four subgroups defined by QTc and basal HR

	QTc <500 ms		QTc ≥500 ms	
	Group A: HR ≥60 b.p.m. ($n = 35$)	**Group B: HR <60 b.p.m. ($n = 39$)**	**Group C: HR ≥60 b.p.m. ($n = 22$)**	**Group D: HR <60 b.p.m. ($n = 14$)**
Age (years) at ECG (range)	43 ± 18 (16–87)	39 ± 17 (15–71)	42 ± 18 (16–77)	39 ± 17 (15–64)
Age (years) at first event (range, number of patients)	25 ± 10 (13–42, $n = 8$)	27 ± 15 (15–71, $n = 19$)	26 ± 19 (15–77, $n = 10$)	26 ± 15 (13–54, $n = 10$)
Female gender [*n* (%)]	23 (66)	22 (55)	16 (73)	9 (64)
Proband [*n* (%)]	8 (23)*	18 (46)	12 (55)	7 (50)
Pore site mutation [*n* (%)]	6 (17)**	11 (28)	10 (46)	7 (50)
Schwarz score	3.1 ± 2.0§	3.6 ± 1.7§	5.5 ± 1.7	6.2 ± 1.2
Syncope or aborted cardiac arrest [*n* (%)]	8 (23)‡	19 (49)†	10 (46)	11 (79)
β-Blockers [*n* (%)]	7 (20)	13 (33)	9(41)	6 (43)

Values are given as the mean ± SD where indicated. HR = heart rate.
*$P < 0.05$ vs. Groups B and C.
**$P < 0.05$ vs. QTc ≥500 ms (Groups C and D).
§$P < 0.001$ vs. QTc ≥500 ms (Groups C and D).
†$P < 0.05$ vs. Group D.
‡$P < 0.05$ vs. HR <60 b.p.m. (Groups B and D).

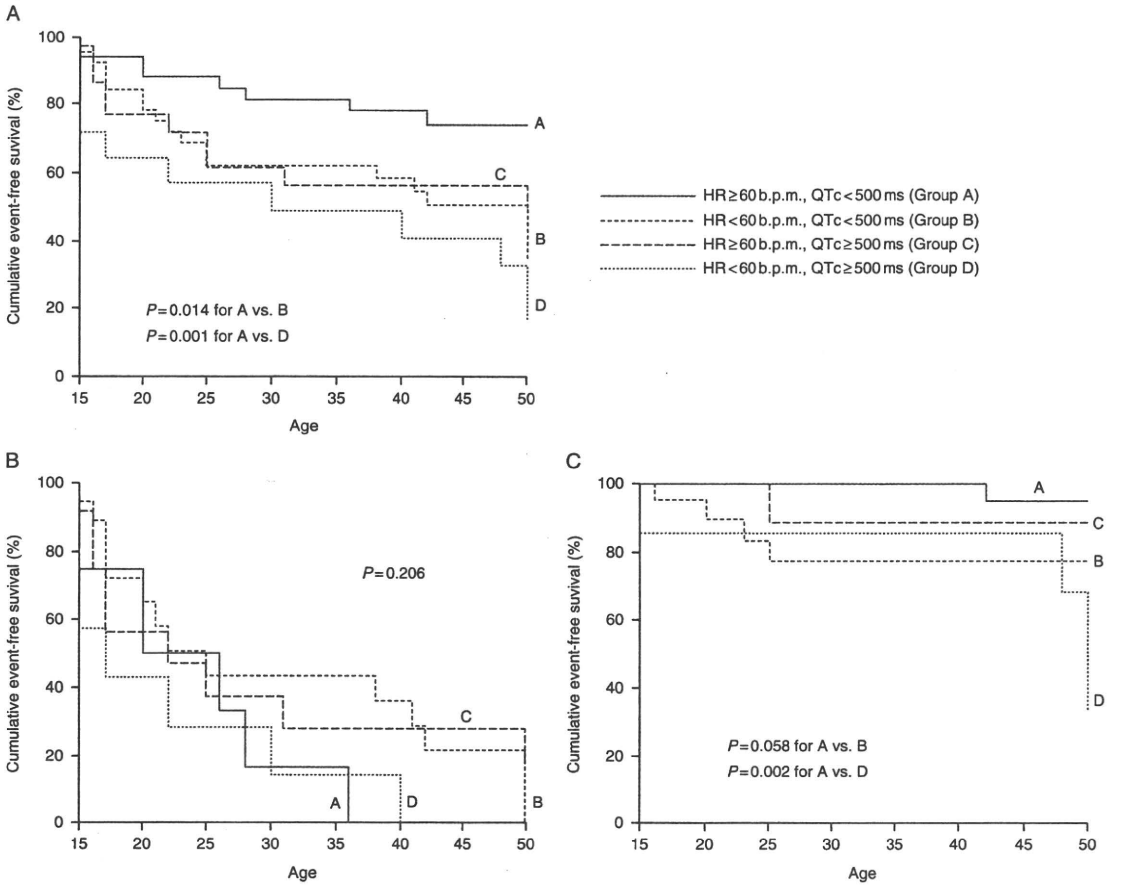

Figure 2 The Kaplan–Meier cumulative cardiac event-free survival curves from the age of 15–50 among each of four subgroups defined by cutoff values for HR of 60 b.p.m. and QTc of 500 ms. *Panels A–C* show the Kaplan–Meier curves of 110 patients, 45 probands and 65 family members, respectively. The group of HR ≥60 b.p.m. and QTc <500 ms was defined as Group A, the group of HR <60 b.p.m. and QTc <500 ms as Group B, HR ≥60 b.p.m. and QTc ≥500 ms as Group C, and HR <60 b.p.m. and QTc ≥500 ms as Group D.

Table 4 Contribution of QTc duration and HR to COX survival model

	Number of patients	Hazard ratio	95% CI	*P*-value
QTc <500 ms				
HR ≥60 b.p.m. (Group A)	35	1	–	–
HR <60 b.p.m. (Group B)	39	2.60	1.14–5.97	0.023
QTc ≥500 ms				
HR ≥60 b.p.m. (Group C)	22	2.16	0.85–5.47	0.105
HR <60 b.p.m. (Group D)	14	4.39	1.76–10.92	0.001

Treatment

β-Blocker therapy was introduced in 35 patients (29 probands) after diagnosis of LQT2 was made. Mean HR on medication was 56 ± 8 b.p.m. Metoprolol was used in 3 patients (90 ± 52 mg, 30–120), carvedilol in 3 (15 ± 9 mg, 5–20), atenolol in 4 (50 ± 0 mg, 50), propranolol in 21 (42 ± 16 mg, 30–80), and bisoprolol in 4 (4 ± 1 mg, 2.5–5).

Implantable cardioverter-defibrillator was implanted in 12 patients (VF: five patients, syncope: seven patients) during the first hospitalization or follow-up. In seven patients with a history of cardiac arrest due to VF (*Table 1*), two patients were treated with an ICD, three with both ICD and β-blocker, one with a pacemaker, and one with β-blocker alone (because the patient rejected ICD implantation). In a patient with a pacemaker, TdP was

observed repeatedly whenever she fell asleep and sinus rhythm became <60 b.p.m. during her first admission to the hospital. After pacemaker implantation, atrial pacing at 80 b.p.m. completely suppressed TdP. None of the patients received surgical left cardiac sympathetic denervation in our study population.

Recurrence of arrhythmic events during follow-up

For the follow-up data, 36 patients (22 patients on BBT) followed more than 3 months were recruited and 86% of patients (31 patients: 18 patients on BBT, 8 patients with an ICD, 10 patients without treatment) completed the mean follow-up period of 50 ± 39 months (40 ± 35 months for 18 patients on BBT and 63 ± 42 months for 13 patients without BBT).

Eighteen subjects on BBT consisted of 14 symptomatic (due to syncope) and 4 asymptomatic patients. Arrhythmic events during follow-up were observed only in symptomatic patients (seven patients: VF was observed in one patient, syncope in six patients). Analysis of the relationship between HR of <60 b.p.m. and recurrent events was also performed. Cardiac events during follow-up were observed in three of nine patients who showed HR <60 b.p.m. before BBT and four of eight patients with HR <60 b.p.m. after BBT ($P = 0.60$ and 0.06, respectively). Therefore, low HR of <60 b.p.m. at rest before or after β-blockers did not predispose ventricular arrhythmia, although the statistical insignificance could be due to a small number of patients for analysis. Details of treatment after recurrence in each individual were described below.

A 16-year-old male patient with a history of syncope experienced VF and was resuscitated. He underwent ICD implantation and dosage of bisoprolol was increased from 2.5 to 5 mg/day, which prevented any cardiac events for a follow-up period of 34.5 months. Recurrent syncope or documented TdP on BBT were observed in six patients: two patients who took metoprolol (one did not comply with the drug regimen and one with a syncopal episode on medication), one patient with atenolol (syncope twice and electrical storm due to TdP twice on medication), and three patients with propranolol (one did not comply with the drug regimen, two experienced a recurrent syncopal episode on medication). In those who did not comply with medication, syncope or TdP was suppressed by resuming BBT. Recurrent episodes of syncope in one patient on metoprolol (120 mg/day) have been suppressed by changing BBT to bisoprolol (2.5 mg/day) for 20 months. Implantable cardioverter-defibrillator implantation was also performed in this patient. Episodes of one patient on atenolol (50 mg/day) were not suppressed with additional prescription of mexiletine (400 mg/day), and ICD was implanted. He experienced an electrical storm after ICD implantation. While adjusting BBT, he was diagnosed with oesophageal cancer and died after 19.8 months follow-up. Syncope in one patient on propranolol (60 mg/day) was suppressed with combined medication of propranolol and diazepam. The other patient on propranolol (30 mg/day) was implanted with an ICD after recurrent episodes of syncope. Atrial pacing of 84 b.p.m. prevented arrhythmic events.

In 13 patients without BBT, 5 were symptomatic (1 VF and 4 syncope) at the first medical contact. In these patients, only one patient with a history of VF experienced an appropriate ICD shock following recurrent VF. To note, pacing using ICD leads was introduced during the first hospitalization in three of five symptomatic patients in whom TdP was repeatedly observed under HR of 60 b.p.m. In these patients, pacing prevented recurrent cardiac events during follow-up.

Discussion

The present study demonstrated that basal HR of <60 b.p.m. was an apparent risk factor for cardiac events in LQT2 patients. Corrected QT ≥500 ms and female gender were also useful for risk stratification in LQT2. The Kaplan–Meier analysis in total study population revealed that cumulative event-free survival was significantly higher in the subgroup with HR ≥60 b.p.m. and QTc <500 ms than in the two groups with HR <60 b.p.m. ($P <$ 0.05). The same trend was observed in the analysis of family members. On the other hand, there was no significant difference in basal HR irrespective of cardiac events in probands. Because, first, the number of probands ($n = 45$) was relatively smaller than that of family members ($n = 65$), and second, there was an entry bias: 84% of probands were referred for genetic testing as they were symptomatic, which influenced the evaluation of basal HR and cardiac events. Our examination of family members therefore suggested that *KCNH2* mutation carriers associated with more severe bradycardia may show a stronger penetrance.

Mutations in *KCNH2* are causative of LQT2, and *KCNH2* encodes for the rapid component of the delayed rectifier K-current (I_{Kr}). In electrophysiological studies, I_{Kr} was shown to be present in rabbit[23] and mouse[24] sinoatrial node cells. Pharmacological inhibition of I_{Kr} by E-4031 markedly suppressed the spontaneous activity of sinoatrial node cells, suggesting that I_{Kr} activation plays a key role in maintaining an adequate HR. In other experimental models,[25] I_{Kr} blockade has also been shown to cause bradycardia. In clinical studies, bradycardia is more frequently observed in LQT2.[3,26] However, no previous studies have demonstrated the validity of bradycardia as a predictor of prognosis.

As for pore site mutations of *KCNH2*, known as a risk factor for cardiac events in LQT2, they were correlated with cardiac events in univariate but not multivariate analysis in our study cohort (*Table 2*). This contrasts with the previous report of Moss *et al.*[10] and is probably due to the difference in the number of studied mutations as well as the exclusion of patients who had their first cardiac events before 15 years old.

β-Blockers are first line therapy for prevention of TdP in LQT2 because it suppresses early afterdepolarizations carried by L-type Ca^{-} channels or Ca^{2+} channels.[27–29] The result of our study, however, may cause concerns that BBT-induced HR-reduction could lead to recurrence of ventricular arrhythmias. To answer the question, we analysed the patient group on BBT during follow-up, but low HR of <60 b.p.m. at rest before or after β-blockers did not predict recurrence of cardiac events ($P =$ 0.60 and 0.06, respectively). Our study cohort may be too small to clarify this issue and therefore, further clinical evaluation with a large number of patients will be required to conclude the significance of low HR on/off β-blockers in LQT2. On the basis of our

findings, however, it is reasonable to hypothesize that pacing could be used as an adjunctive therapy in LQT2 patients showing HR <60 b.p.m. irrespective of QTc values. Our combined risk-evaluating scales (*Figure 1*) would help physicians estimate long-term therapy in asymptomatic *KCNH2* mutation carriers, both probands and family members.

Limitations

In some symptomatic patients, there was a long period between the average age at onset of symptoms and the average age at ECG recording. Regarding this issue, the risk evaluation should be carefully considered. In addition, it was difficult to gather ECG recordings of the first event, because many patients suffered syncope without a doctor witnessing the first event. However, among the four subgroups, there was no significant difference in age at ECG recording and age at the first event (*Table 3*). Therefore, we evaluated cardiac risk using the HR recorded by ECG at the first medical contact. As for the effect of BBT on HR as a risk factor for cardiac events, our cohort was too small to lead a relevant conclusion because follow-up of patients was insufficient. Hence, it awaits a further study with a larger number of genotyped LQT2 patients.

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Conflict of interest: none declared.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Predictors of Electrical Storm in Patients With Idiopathic Dilated Cardiomyopathy

– How to Stratify the Risk of Electrical Storm –

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Background: Electrical storm (ES) is a serious problem in patients with an implantable cardioverter defibrillator (ICD). However, insufficient reports have indicated the predictors of ES in ICD patients with idiopathic dilated cardiomyopathy (DCM). The purpose of this study was to clarify the predictors of ES for risk stratification in DCM patients with an ICD.

Methods and Results: Of 446 ICD patients, 53 DCM patients were included in this study. During a mean follow-up of 55±36 months, ES (≥3 times appropriate ICD therapy within 24 h) occurred in 18/53 (34%) patients. According to multivariate Cox proportional hazard regression analysis, a duration of the terminal low amplitude signals of <40 μV (LAS40) (HR 1.4/10 ms increase, 95% confidence interval (CI) 1.1–2.1; P=0.0049) or root mean square voltage of the last 40 ms of the QRS complex (RMS40) (HR 0.88/1 μV, 95%CI 0.77–0.96; P=0.001) on the signal averaged electrocardiogram, and a history of atrial fibrillation (AF) before ICD implantation (HR 2.3, 95%CI 1.2–5.0; P=0.013) were independently associated with an increased risk of ES.

Conclusions: Our data indicated that a longer LAS40, lower RMS40 and history of AF before ICD implantation could strongly predict ES, and the combination of those parameters could effectively stratify the risk of ES in DCM patients. (*Circ J* 2010; **74:** 1822–1829)

Key Words: Dilated cardiomyopathy; Electrical storm; Implantable cardioverter defibrillator; Signal averaged electrocardiogram; Ventricular tachyarrhythmias

Implantable cardioverter defibrillators (ICDs) have a high success rate in terminating life-threatening ventricular arrhythmias, including ventricular tachycardia (VT) or ventricular fibrillation (VF), and have become an established therapeutic option for reducing the risk of sudden cardiac death.[1,2] In primary prevention, 21% of patients receive the benefit of ICD with an appropriate therapy within 5 years as shown in the SCD-HeFT trial,[3] whereas in secondary prevention, this is the case for as many as 69–85% patients within 3 years as shown in the AVID trial.[4] However, some patients receive multiple shock therapies in a short period, which is referred to as an electrical storm (ES).[5] Although the incidence of ES is only 4% when ICDs are implanted for primary prevention according to the MADIT II trial,[6] and 10–28% over a 1- to 3-year follow-up period for secondary prevention.[1,7–9]

Since there has been an increase in ICD indications, ES has become an important issue because of all the clinical, psychological and economical consequences involved. Although several studies have reported the incidence, predictive factors and clinical prognosis of ES in patients with coronary artery disease, sufficient data does not exist regarding idiopathic dilated cardiomyopathy (DCM). The purpose of this study was to clarify the predictors and prevalence of ES for risk stratification in DCM patients with an ICD.

Methods

Study Population

Among our cohort of 446 ICD patients, 53 consecutive DCM patients (41 men and 12 women, mean age 55±15 years) who received an ICD between 1990 and 2004 at the National

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Cardiovascular Center, Suita, Japan, were included in this study. The following devices were implanted: Medtronic 7217B, 7217D, 7220C, 7221CX, 7223CX, 7227CX, 7229CX, 7271, 7273, 7278 and CPI/Guidant 1600, 1715, 1742, 1790, 1861. We recorded a detailed patient history including any prescriptions and evaluated his/her 12-lead electrocardiogram and transthoracic echocardiogram with doppler screening. The signal-averaged electrocardiogram (SAECG) (Arrhythmia Research Technology model 1200 EPX, Austin, TX, USA) was also examined. This system constituted a vector magnitude with a bidirectional bandpass filter setting of 40–250 Hz combined with the standard bipolar orthogonal (X, Y, Z) leads. Signal averaging of 200–300 beats was performed to obtain a diastolic noise level of <0.5 μV. The onset and offset of the QRS complex were determined by an algorithm that calculated the total QRS duration (TQRSD), root mean square voltage of the last 40 ms of the QRS complex (RMS40) and the duration of the terminal low amplitude signals of <40 μV of the QRS complex (LAS40). Coronary angiography was performed in all patients to rule out ischemic cardiomyopathy. Endocardial biopsy was conducted in 42 patients after obtaining informed consent. The left ventricular ejection fraction (LVEF) was assessed by using radionuclide scanning or left ventriculography. Patients with diffuse left ventricular dysfunction and enlargement of the left ventricle were defined as having DCM when coronary artery disease, valvular disease, or any other cardiomyopathy was excluded.

The study patients received an ICD for secondary prevention of sudden cardiac death after 1 or more episodes of confirmed sustained ventricular tachyarrhythmias or under the context of any presumed tachyarrhythmic syncopal attacks with induction of VT/VF during an electrophysiological study. Single-chamber devices were implanted in 24 (42%) patients and 29 (58%) patients had dual-chamber devices. The ICD was programmed according to the documented or induced arrhythmia with at least 2 detection zones. The lowest VT-detection zone had a cycle length of 419±55 ms. In the VT-zone, anti-tachycardia pacing including more than 1 burst pacing and/or 1 ramp pacing therapy followed by cardioversion were programmed, whereas maximum shocks were programmed in the VF-zone.

Table 1. Baseline Characteristics of the Study Population (n=53)

Clinical characteristics	
Age (years)	55±15
Gender (male) (%)	41 (77%)
BMI (kg/m^2)	21±2.9
NYHA classification	1.8±0.8
Creatinine clearance (ml/m)	74±29
Hospitalization for preceding HF (%)	29 (55%)
History of AF before ICD implantation (%)	17 (32%)
Monomorphic VT as index arrhythmia (%)	35 (66%)
LVEF (%)	27±10
Baseline ECG	
QRS-width (ms)	129±40
QT-intervals (ms)	494±67
Signal-averaged ECG	
TQRSD (ms)	158±48
LAS40 (ms)	55±28
RMS40 (μV)	18.7±17.7
Echocardiography	
LADs (mm)	41±9
LVDd (mm)	67±10
LVDs (mm)	56±12
Medication	
β-blocker (%)	43 (81%)
Amiodarone (%)	27 (56%)
Digitalis (%)	25 (47%)
Spironolactone (%)	25 (47%)
ACE-inhibitor (%)	40 (75%)
Diuretics (%)	38 (72%)
Class I antiarrhythmics (%)	5 (9%)

BMI, body mass index; NYHA, New York Heart Association; HF, heart failure; AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; TQRS, total filtered QRS duration; LAS40, the duration of the terminal low (<40 μV) amplitude signals; RMS40, the root mean square voltage of the last 40 ms; LADs, left atrial diameter of end-systole; LVDd, left ventricular diameter of end-diastole; LVDs, left ventricular diameter of end-systole; ACE, angiotensin-converting enzyme.

Definition of ES and Data Collection

For the purpose of this analysis, we defined ES as the occurrence of at least 3 separate episodes of VT/VF terminated by an ICD intervention within a 24-h period.[8] ICD interventions included antitachycardia pacing, low-energy shocks and high-energy shocks. Repetitive ineffective shocks were not categorized as ES. The follow-up began after the implantation and ended in December 2004. The patients visited the ICD outpatient clinic routinely every 3–6 months and were encouraged to schedule additional visits whenever shocks, palpitations, syncope or pre-syncope had occurred. During each visit, the device was interrogated to evaluate the number and type of episodes with the stored electrograms. In the cases with ES, the patient was admitted to the hospital and blood samples (electrolytes, blood cell count, thyroid, creatinine levels, C-reactive protein, creatinine kinase and troponin), echocardiography and coronary angiography were performed if necessary to investigate the causes.

Statistics

P-values of less than 0.05 were considered statistically significant. The results are expressed as frequencies and percentages for categorical variables and median or mean±SD for numerical variables. Univariate Cox proportional hazards models were used to assess the significance of baseline variables with respect to the outcome. Parameters with P<0.10 by univariate analysis were included in a Cox proportional hazards multivariate regression analysis and then adjusted for age, sex, left ventricular diastolic diameter (LVDd) and LVEF. The relationship between the clinical predictors and the occurrence of ES were analyzed by means of survival analysis techniques. The survival function was computed as the time of the implantation to the occurrence of ES. The observation was censored at the time of the last known follow-up or time of death, when ES did not occur. Event-free survival curves were calculated according to the Kaplan-Meier method. The relationship between the occurrence of ES and the prognosis was similarly analyzed. A log rank test was used to determine whether significant differences existed between the curves. A statistical analysis was performed using JMP 5.1 software.

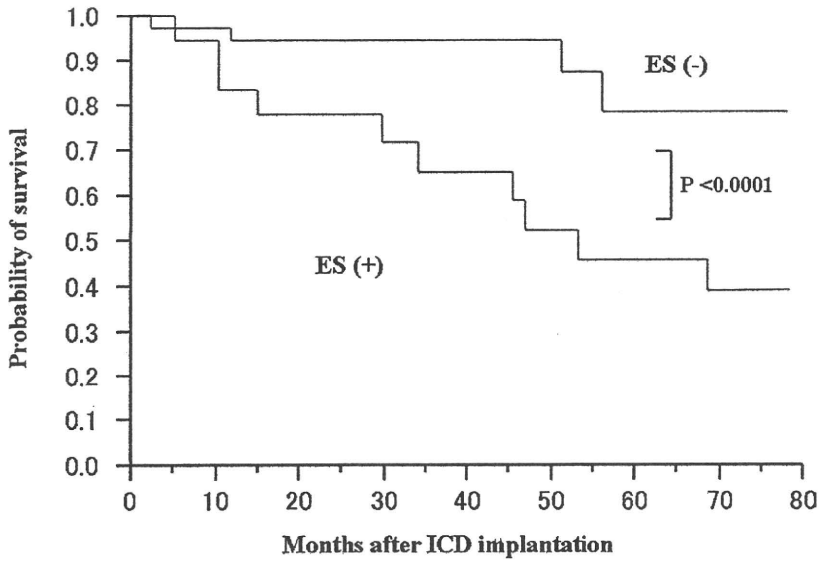

Figure 1. The cumulative probability of survival for dilated cardiomyopathy patients with electrical storm (ES) and those without ES. There was a significant difference in survival between the 2 groups (P<0.0001). ICD, implantable cardioverter defibrillator.

Table 2. Comparison of Baseline Characteristics Between the Patients With ES and Without ES

Patients	Patients with ES (n=18)	Patients without ES (n=35)	Univariate analysis P-value	Multivariate analysis P-value (HR, 95%CI)	Multivariate analysis P-value (HR, 95%CI)
Clinical characteristics					
Age (years)	56.6±14.2	53.6±15.7	0.23		
Sex (male) (%)	14 (77.8%)	27 (77.1%)	0.91		
BMI (kg/m²)	20.5±2.10	21.9±3.0	0.11		
NYHA classification	2.1±0.8	1.7±0.8	0.058		
Creatinine clearance (ml/m)	78.9±28.6	72.0±28.6	0.82		
Hospitalization for preceding HF (%)	13 (72%)	16 (46%)	0.041		
History of AF before ICD implantation (%)	11 (61%)	6 (17%)	0.0004	0.021 (HR 2.2, 95%CI 1.1–4.5)	0.015 (HR 2.4, 95%CI 1.2–5.7)
Monomorphic VT as index arrhythmia (%)	15 (83%)	20 (57%)	0.04		
LVEF (%)	27.0±9.6	27.3±11.8	0.97		
Baseline ECG					
QRS-width (ms)	137±40	125±39	0.12		
QT-duration (ms)	494±57	496±73	0.87		
Signal-averaged ECG					
TQRSD (ms)	180±47	147±42	0.022		
LAS40 (ms)	76.8±18.3	43.8±24.9	0.0003	0.0049 (HR 1.4/10ms increase, 95%CI 1.1–2.1)	–
RMS40 (μV)	5.2±3.1	25.9±18.4	<0.0001	–	0.0010 (HR 0.88/1 μV increase, 95%CI 0.77–0.96)
Echocardiography					
LADs (mm)	41.4±9.3	40.4±9.2	0.46		
LVDd (mm)	69.8±10	65.6±9.5	0.11		
LVDs (mm)	59.3±10.2	54.8±12.5	0.11		
Medication					
β-blocker (%)	14 (78%)	29 (83%)	0.57		
Amiodarone (%)	7 (39%)	20 (57%)	0.39		
Digitalis (%)	9 (50%)	16 (46%)	0.59		
Spironolactone (%)	9 (50%)	16 (46%)	0.59		
ACE-inhibitor (%)	13 (72%)	27 (77%)	0.84		
Diuretics (%)	15 (83%)	23 (66%)	0.12		
Group I antiarrhythmics (%)	2 (11%)	3 (9%)	0.16		

ES, electrical storm; HR, hazard ratio; CI, confidential interval; TQRSD, TQRS duration. Other abbreviations see in Table 1.

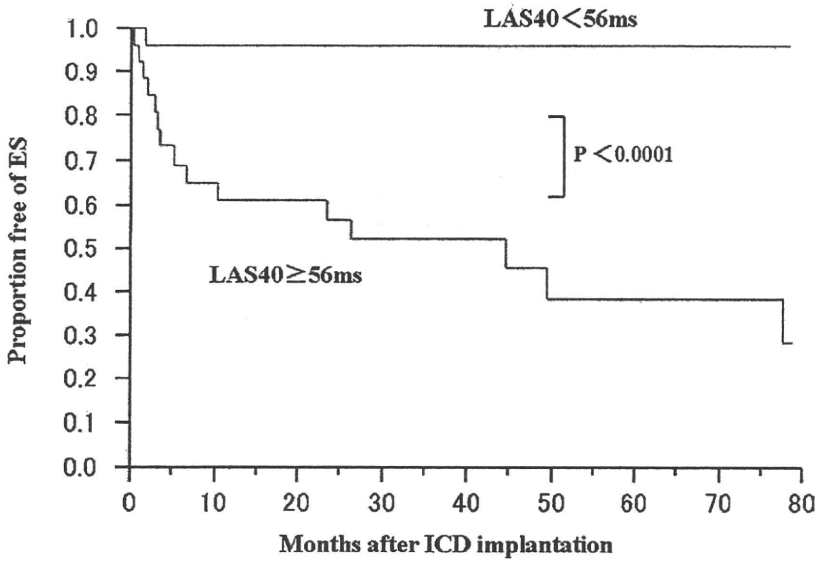

Figure 2. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without terminal low amplitude signals of <40 μV (LAS40) ≥56 ms. The DCM patients with LAS40 ≥56 ms had a significantly higher risk of ES occurrence compared with those with LAS40 <56 ms (P<0.0001). ICD, implantable cardioverter defibrillator.

Results

Baseline Characteristics

The baseline characteristics of the 53 consecutive DCM patients are outlined in **Table 1**. All patients received ICD as a secondary prevention. At the time of implantation, the patients were 55±15 years old. They had a mean LVEF of 27% (9–50%) and a mean LVDd of 67 mm (52–94 mm). The mean NYHA class at the time of the ICD implantation was 1.8±0.8 and the creatinine clearance was 74±29 ml/min. Seventeen (32%) patients had a history of atrial fibrillation (AF). Before ICD implantation, spontaneous VTs were documented in 35 (66%) patients and VF in the remaining 20 (34%) as index arrhythmias. Inappropriate shock therapies were observed in 14 (26%) patients due to sinus tachycardia in 8 (15%) patients, AF in 4 (7.5%) patients and other reasons in 2 (3.5%) patients. As for the medications, β-blockers were prescribed in 43 (81%) patients and amiodarone in 27 (56%).

ES

During a mean follow-up of 52±34 months (median 46 months, range 2–158 months), a total of 18 (34%) patients experienced at least 1 ES episode (median 2 ES episodes per patient). Eleven (61%) patients of the 18 patients with ES experienced 2 or more ES episodes. In 5 (27%) patients, ES was the first episode of an appropriate ICD therapy. The mean duration between the first ES occurrence and ICD implantation was 24±31 months. Three (17%) patients had an exacerbation of their heart failure and the other patients had "extrinsic" causes: 3 (17%) patients had diarrhea or a low potassium level, 2 had an infection and 1 had discontinued the drug therapy. However, no clinical cause could be identified in 9 (50%) patients.

Figure 1 shows the cumulative probability of survival in the DCM patients with ES and in those without ES. As demonstrated, there was a significant difference in the survival between the 2 groups (P<0.0001) and the cumulative mortality for the DCM patients with ES after 60 months was 59%.

Risk Factors for ES

Table 2 shows the baseline characteristics of the subjects with and without ES, and the result of univariate and multivariate analysis. Using a univariate Cox proportional analysis, the NYHA classification at the time of the ICD implantation, history of any previous heart failure, history of AF before ICD implantation, monomorphic VT as index arrhythmia and the parameters on SAECG including LAS40, RMS40 and TQRSD showed the significant association with ES. The correlation between RMS40 and LAS40 was so strong that we were not able to include these 2 parameters in the multivariate analysis simultaneously. When we included LAS40 in the multivariate analysis, a history of AF before ICD implantation and a longer duration of LAS40 remained (P=0.021 and 0.0049, respectively), and when we included RMS40 in the multivariate analysis, a history of AF before ICD implantation and a lower value of RMS40 remained as the significant predictors of ES occurrence (P=0.015 and 0.001, respectively), after adjustment for age, sex, LVDd and LVEF. No independent significant relationships were observed between NYHA classification at the time of the ICD implantation, history of any previous heart failure, monomorphic VT as index arrhythmia or value of TQRSD and the occurrence of ES.

Predictors of ES

Using a sensitivity-specificity analysis utilizing a receiver operating characteristic curve, the cut-off value of LAS40 and RMS40 was set at 56 ms and 11.7 μV to optimize the capability to predict ES. In cases with a cut-off value of LAS40 setting at 56 ms and RMS40 at 11.7 μV, using LAS40 predicted ES with a sensitivity of 94% and specificity of 74%. The areas under the curve of LAS40 at 56 ms was slightly larger than that of RMS40 at 11.7 μV (0.87 vs 0.84, respectively). The Kaplan-Meier curves of the freedom from ES event between the group with or without LAS40 ≥56 ms are illustrated in **Figure 2**. The DCM patients with LAS40 ≥56 ms had a significantly higher risk of ES occurrence compared with those with LAS40 <56 ms (P<0.0001). The Kaplan-Meier curves of the freedom from ES event between

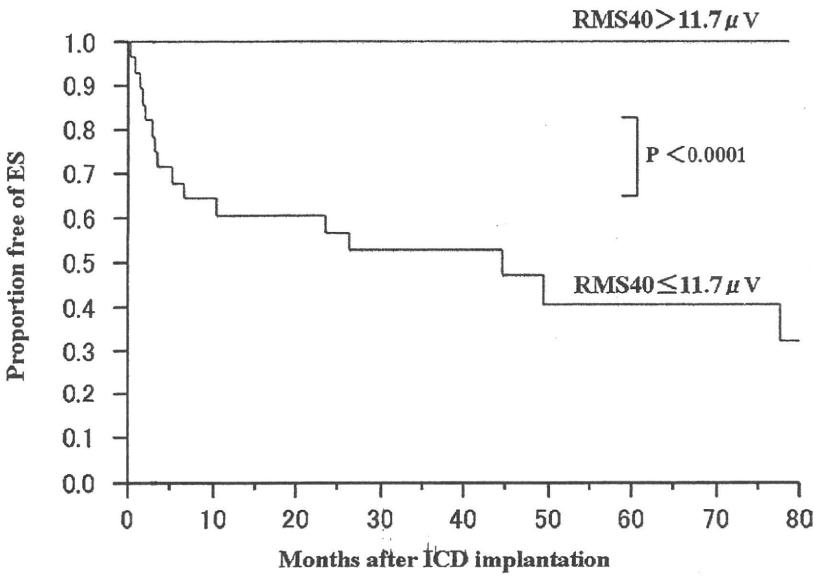

Figure 3. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without root mean square voltage of the last 40ms of the QRS complex (RMS40) ≤11.7 μV. The DCM patients with RMS40 ≤11.7 μV had a significantly higher risk of ES occurrence compared with those with RMS40 >11.7 μV (P<0.0001). ICD, implantable cardioverter defibrillator.

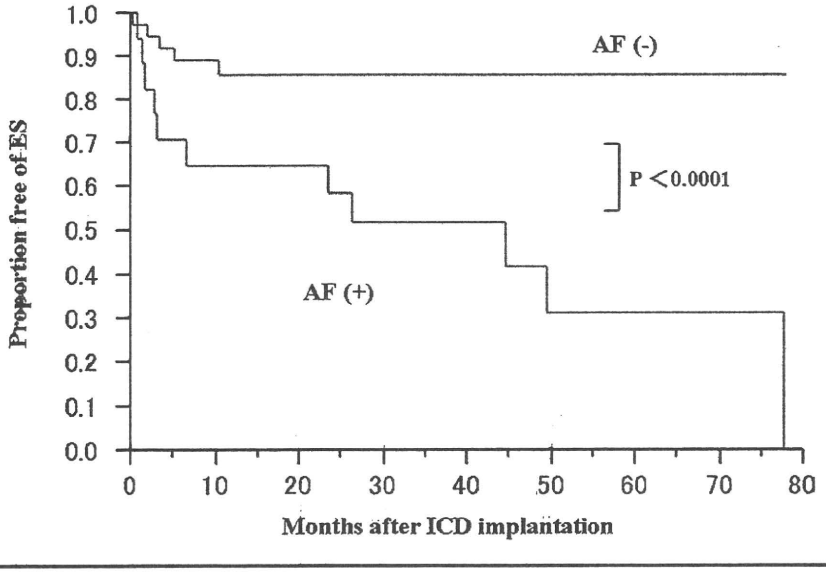

Figure 4. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without a history of atrial fibrillation (AF) before an implantable cardioverter defibrillator (ICD) implantation. The DCM patients with a history of AF before ICD implantation had a significantly higher risk of ES occurrence compared with those without a history of AF before ICD implantation (P<0.0001).

the group with or without RMS40 ≤11.7 μV are shown in **Figure 3**. The DCM patients with RMS40 ≤11.7 μV had a significantly higher risk of ES occurrence compared with those with RMS40 >11.7 μV (P<0.0001). Furthermore, the Kaplan-Meier curves of the freedom from ES event between the groups with and without a history of AF before ICD implantation showed that the DCM patients with a history of AF before ICD implantation had a significantly higher risk of ES occurrence compared with those without a history of AF before ICD implantation (P<0.0001) (**Figure 4**). Atrial fibrillation plus 2 of the following parameters could significantly predict the occurrence of ES: SAECG, LAS40 ≥56 ms or RMS40 ≤11.7 μV. As **Figure 5** shows, when using the combination of these independent predictors (AF and LAS40 ≥56 ms, or AF and RMS40 ≤11.7 μV), the study population could be stratified into 3 groups according to the risk of ES before the implantation.

Discussion

The main finding of our study was that both the quantitative value of the SAECG, especially the value of LAS40, RMS40 and a history of AF before ICD implantation could independently predict the occurrence of ES.

SAECG as a Predictor of ES

Regarding the SAECG, longer LAS40 and lower RMS40 remained a significant index for predicting the occurrence of ES by multivariate analysis, although all 3 parameters on the SAECG; longer LAS40, lower RMS40 and longer TQRSD, were significant by univariate analysis. The risk of ES increased by 40% for each additional 10 ms increase in the value

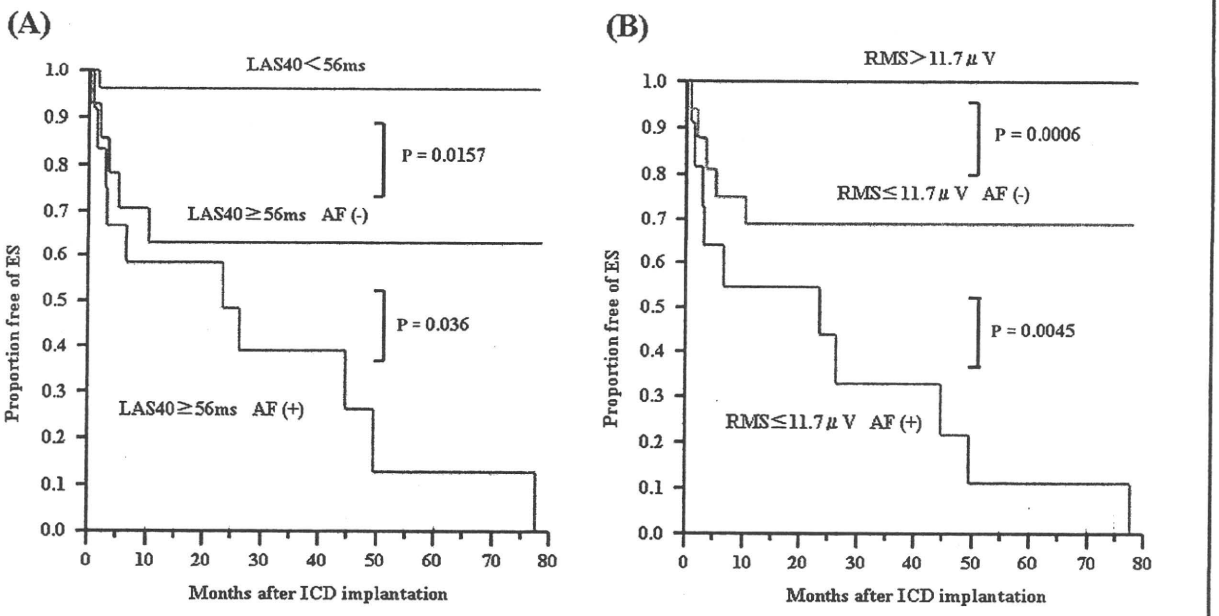

Figure 5. The risk stratification for electrical storm (ES) events with the combination of terminal low amplitude signals of <40 μV (LAS40) or root mean square voltage of the last 40 ms of the QRS complex (RMS40) and a history of atrial fibrillation (AF) before implantable cardioverter defibrillator (ICD) implantation. The combination of (**A**) LAS40 ≥56 ms and a history of AF before ICD implantation or (**B**) RMS40 ≤11.7 μV and a history of AF before ICD implantation could stratify the risk of ES events.

of LAS40 (HR 1.4/10 ms increase, 95% confidence interval (CI) 1.1–2.1; P=0.0049). The optimized cut-off value of LAS40 determined from the receiver operating characteristic curve for differentiating the patients with ES from those without ES was 56 ms, which gave a sensitivity of 94%, specificity of 74%, positive predictive value of 65% and negative predictive value of 96%. In contrast, the risk of ES decreased by 12% for each additional 1 μV increase in the value of RMS40 (HR 0.88/1 μV, 95%CI 0.77–0.96; P=0.001). The optimized cut-off value of RMS40 determined from the receiver operating characteristic curve for differentiating the patients with ES from those without ES was 11.7 μV, which gave a sensitivity of 100%, specificity of 71%, positive predictive value of 61% and negative predictive value of 100%. We used the optimized cutoff value of LAS40 as 56 ms and RMS40 as 11.7 μV to stratify the risk of ES. However, the cut-off value of LAS40 was usually set at 38 ms and RMS40 at 20 μV. We also evaluated the significance of the SAECG for predicting the occurrence of ES by using the cut-off value of LAS40 at 38 ms and RMS40 at 20 μV, and it was possible to differentiate the patients with ES from those without ES by using these classical values as well.

Although the significance of the SAECG as a predictor of ES has never been reported thus far, there have been several reports that have indicated the significance of the SAECG as a predictor of ventricular tachyarrhythmias or the prognosis in DCM patients.[10–16] Goedel-Meinen et al reported that an abnormal SAECG was an independent indicator for sudden cardiac death (3.7-fold risk), the total cardiac mortality (2.1-fold risk) and any cardiac events (2-fold risk) in patients with DCM using a multivariate analysis.[12] Mancini et al showed the effectiveness of SAECG as an independent predictor of end points including death, urgent transplant and VT in patients with non-ischemic congestive cardiomyopathy and relative risk estimate (actually an odds ratio) for abnormal vs normal SAECG was 16.7:1 for these events in this report.[10]

The SAECG is a modality for assessing the existence of ventricular late potentials, which indicate an arrhythmic substrate, especially depolarization abnormalities, leading to sustained ventricular tachyarrhythmias. In general, ventricular late potentials may be defined as low-amplitude fractionated activity appearing at the end of QRS and extending into the ST-segment. Fragmented electrocardiograms are thought to be found when myocardial fibers are separated by connective tissue. Moreover, a close correlation between the presence of continuous fractionated electrical activity and the perpetuation of VT has been demonstrated.[17,18] The extent of the myocardial fibrosis also appears to be correlated with an abnormal SAECG. Yamada et al reported that patients with biopsy-proven marked fibrosis exhibited a longer TQRSD and lower LAS40 than did the patients with less fibrosis, although those patients had no differences in the left ventricular end-diastolic dimension and ejection fraction.[19] This relation was also confirmed in a study by Konta et al, which demonstrated that patients with DCM had abnormal thallium perfusion images.[20] These principles could support the theory that the late potentials could contribute to the maintenance of the electrical instability, thus increasing the possibility of the occurrence of ES. The myocardium in the patients with ES would be more damaged with more severe late potentials, and thus the conventional cut-off value (TQRSD >120 ms, RMS40 <20 μV and LAS40 >38 ms) would not be adequate for specifically predicting ES.[21–25]

A History of AF Before ICD Implantation as a Predictor of ES

Our study showed that a history of AF before ICD implantation was a strong independent predictor of the occurrence of ES (HR 2.3, 95%CI 1.2–5.0; P=0.013). Although there have

been no reports assessing the significance of a history of AF before ICD implantation as a predictor of ES thus far, its significance as a predictor of ventricular arrhythmias has been reported in previous studies.[26–28] Moreover, Grimm et al reported that AF, the LVEF and a history of VT/VF before an ICD implantation were the predictors for an appropriate ICD intervention in DCM patients during 36 months of follow-up.[29]

Because ES is considered to be one of the most severe cases of ventricular tachyarrhythmias, it is not unreasonable that AF could be one of the predictors of ES as the result of our study. There are several possible explanations for the association between a history of AF before ICD implantation and ventricular tachyarrhythmias including ES. First, a rapid ventricular rate during AF will directly reduce the ventricular refractoriness and, moreover, the irregular rhythm during both paroxysmal and persistent AF leads to a high incidence of short-long-short sequences, which could have a pro-arrhythmic effect. Second, AF decreases the cardiac output and increases the filling pressure through the loss of an atrial effective contraction and decreased diastolic time, which could affect the electrophysiological properties. Third, AF could trigger ischemia, through a tachycardia, also leading to a reduction in the cardiac output and increasing the left ventricular filling pressure or directly changing the electrophysiological properties of the ventricles.[27,30–34]

To the best of our knowledge, the only study that referred to ES with DCM patients was published by Bansch et al.[1] They reported that the presence of NYHA III heart failure before an ICD implantation, low LVEF (<40%), a history of monomorphic VT or inducibility of monomorphic VT, especially that with a superior axis, were the best predictors of ES in patients with DCM.[1] Unlike that study, the LVEF did not remain as a significant risk factor in the present study. The baseline LVEF was tightly distributed at much lower levels between the 2 groups with and without ES in our study, so that the difference in the LVEF between each patient could fall into obscurity. Although heart failure and monomorphic VT remained as significant predictors of ES by univariate analysis, they did not remain so by multivariate analysis. The difference in the study population, the severity of any underlying disease or the definition of ES could be part of the reason for the discrepancies with previous studies.[1,8,35,36]

Potential Approaches to Prevent ES

Potential approaches were considered to prevent ES. First, recent reports revealed that novel empiric ablation techniques for substrate modification and prevention of VT/VF could reduce the ICD therapy,[37,38] and cardiac resynchronization therapy could reduce the incidence of VT due to reverse remodeling.[39,40] Pulmonary vein isolation may be 1 of the options to prevent ES by suppression of AF.[41]

Study Limitations

First, the retrospective observational design was a major limitation of our study. Furthermore, the accurate classification of shocks as being appropriate or inappropriate remains a problem, especially for patients with a single-chamber ICD. Because patients with a history of AF before ICD implantation were more likely to have single-chamber ICDs, there may have been more false positive events in the history of the AF group. However, the ICD electrograms were carefully examined by 2 expert electrophysiologists blindly to confirm that inappropriate therapy was not a trigger of these ESs and to determine the appropriateness of the ICD shocks.

Second, because the number of patients in the study group was small, the statistical power of the patient group analyses may therefore be limited. However, the study group was relatively homogeneous because all consecutive secondary prevention patients were included.

Third, cardiac resynchronization therapy with a defibrillator function should be used in our study population, which would reduce the occurrence of ES at this moment. However, cardiac resynchronization therapy with a defibrillator function was not available in Japan back then.

Conclusion

ESs occur frequently in ICD patients with DCM. The major predictors of ES were a longer LAS40, a lower RMS40 and a history of AF before ICD implantation. The combination of these indices could effectively stratify the risk of ES prior to the ICD implantation.

Disclosure

Conflict of interests and statement: no financial support from a specific company was given and there was no conflict of interest or specific unapproved usage of any compound or product.

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Enlargement of Acute Intracerebral Hematomas in Patients on Long-Term Warfarin Treatment

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Key Words
Intracerebral hemorrhage · Hematoma enlargement · Warfarin · Mortality

Abstract
Background: The relationship between warfarin administration and the frequent development of enlarged hematomas in patients with acute intracerebral hemorrhage (ICH) is controversial. The present study was carried out to examine this issue. ***Methods:*** This study reviewed 41 patients with nontraumatic ICH within 24 h after stroke onset from 1999 to 2003 who received long-term warfarin treatment (29 men and 12 women, 70 ± 12 years old) and 323 patients who had not been on warfarin (177 men and 146 women, 66 ± 13 years old). The hematoma volume (HV) on admission, final HV, frequency of hematoma enlargement (HE) and other background characteristics were investigated. ***Results:*** Both the HV on admission ($p = 0.031$) and final HV ($p = 0.001$) were larger in patients on warfarin than in those not receiving warfarin. HE occurred more frequently ($p < 0.001$), and mortality at 30 days or at discharge was higher ($p = 0.003$) in the warfarin group than in the control group. A multivariate adjusted logistic regression analysis showed that warfarin treatment (OR = 5.75, 95% CI = 2.41–13.8, $p < 0.001$), liver disease (OR = 2.59, 95% CI = 1.12–5.99, $p = 0.026$), and the National Institutes of Health Stroke Scale score (OR = 1.10, 95% CI = 1.04–1.15, $p < 0.001$, per 1-score increase) on admission were independently related to HE. ***Conclusions:*** Acute ICH in patients on long-term warfarin treatment appears to be associated with HE.

Introduction

A spontaneous intracerebral hemorrhage (ICH) is one of the most serious hemorrhagic complications associated with warfarin treatment. Oral anticoagulant therapy with warfarin not only increases the risk of ICH, but also worsens ICH outcomes [1–8]. It is unclear whether hematoma enlargement (HE) occurs more frequently or the final hematoma volume (HV) is greater in patients with acute brain hemorrhage who are on long-term warfarin treatment. Wintzen et al. [1] found no differences in the rate of progression, mortality or degree of recovery between patients with anticoagulant-associated hemorrhage and those with spontaneous intracranial hemorrhage. However, Franke et al. [3] demonstrated that the volume of the supratentorial hematoma was significantly greater in patients on anticoagulant treatment than in those not on anticoagulant therapy. Flibotte et al. [5]

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showed that hematoma expansion occurred more frequently in patients on warfarin than in those not on warfarin, and that hematoma expansion was associated with a trend toward increased 3-month mortality. Flaherty et al. [9] reported that warfarin use was associated with larger initial ICH volume when international normalized ratio (INR) values were >3.0; the results concerning HE were uncertain. The differences in these studies' results may be due to differences in the site and cause of bleeding, as well as the intensity of warfarin treatment.

To elucidate the relationship between hematoma size and long-term anticoagulant therapy, the HV and background characteristics of patients treated with warfarin were compared with those of patients not on warfarin. In addition, the clinical course of ICH patients on long-term warfarin therapy during the acute stage was compared to that of patients not on warfarin.

Methods

In this study, 424 consecutive patients with nontraumatic ICH who were admitted to the cerebrovascular division within 24 h after stroke onset from January 1999 to December 2003 were assessed. Patients were selected from the prospectively recorded database that included all inpatients admitted to the stroke care unit. Any patients with ICH due to an aneurysmal rupture, vascular malformations, hemorrhagic transformation after brain infarction and brain tumor, as well as those who experienced a hemorrhage primarily into the ventricles were excluded. Of the 424 patients, 60 were ineligible because they had been on antiplatelet therapy but not on anticoagulant therapy, and were thought not to be appropriate for the control group. The remaining 364 patients (206 men and 158 women, aged 66 ± 13 years) were therefore enrolled in the present study.

The medical records and computed tomography (CT) scans of the 41 patients who had been on long-term warfarin treatment (warfarin group) and the 323 patients who had not been on warfarin (control group) were reviewed. The first CT examination was performed exactly on admission, the second CT scan was performed routinely within 24 h after admission, and the third CT scan was performed within a few days after the second CT scan. Additional CT scans were performed if a patient deteriorated clinically. We reviewed the time interval from ICH onset to the first CT scan and the time interval from onset to the follow-up CT scan used for the determination of HE. The location, number, shape and volume of the hematomas as well as the presence of ventricular bleeding were noted. The locations of the hematomas were classified as putaminal, thalamic, combined, lobar, pontine, cerebellar, or other locations. All CT scans were reviewed and evaluated by neuroradiologists and neurologists who were blinded to the patients' clinical status. The time of ICH onset was defined as the time when the subject or a companion reported the acute onset of a neurological deficit. When the time of onset could not be clearly specified, the time that the subject was last known to be normal was taken as the time of onset.

The ICH volume was determined as follows [10–13]. The longest diameter (A) and the longest diameter (B) perpendicular to A were measured on CT films of the slices showing the largest ICH area. The height of the hematoma (C) was calculated by multiplying the number of slices involved by the slice thickness. To obtain the ICH volume, the 3 diameters were multiplied and then divided by 2 ($A \times B \times C/2$). Hemorrhage volume within the ventricular system was not assessed. The parenchymal hemorrhage was considered to have enlarged when the volume on the follow-up CT was 1.4-fold larger than the volume observed on the admission CT [14].

Admission HV, final HV, frequency of HE, and other baseline characteristics, such as age, gender, hypertension (a history of antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l, positive 75-gram oral glucose tolerance test, or a history of antidiabetic medication and insulin), hypercholesterolemia (serum total cholesterol ≥5.69 mmol/l or a history of antihypercholesterolemic medication), previous symptomatic ICH, previous symptomatic ischemic stroke, heart disease (including arrhythmia), liver disease (including cirrhosis, active hepatitis, alcoholic liver damage, and fatty liver), smoking habit (previous and current), and drinking habit (≥2 drinks per day) were compared between the two groups. In addition, the patients' systolic blood pressure, diastolic blood pressure, blood glucose, and INR for prothrombin time on admission were also assessed. In the acute stage, all patients had their systolic and diastolic blood pressures measured every 6 h after admission.

Each patient's neurological state was evaluated by a neurologist. The neurological deficits on admission were evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. The clinical outcome was assessed using the modified Rankin Scale (mRS, grades 0–5) at 30 days or at discharge, whichever occurred sooner [15]. Death was assigned an mRS score of 6 [16].

Values are expressed as mean ± SD or median and interquartile range. The clinical characteristics of ICH patients on warfarin were compared to those of the ICH patients not on warfarin using the χ^2 test, unpaired Student's t test, and the Mann-Whitney U test as appropriate. A p value less than 0.05 was considered to be significant. The background characteristics of patients with and without HE were compared. To identify the independent predictors for HE, a multivariate logistic regression analysis with adjustments for age and gender was conducted using the clinical characteristics that showed a significant ($p < 0.05$) or a marginally significant ($0.05 \leq p < 0.1$) correlation with each indicator as independent variables based on univariate analyses.

Results

Thirty-six patients in the warfarin group were on warfarin only, and 5 were on both warfarin and antiplatelet therapy. The underlying diseases that required anticoagulation included: nonvalvular atrial fibrillation in 22 patients; mitral or aortic valve replacement in 7; deep vein thrombosis in 4; dilated cardiomyopathy in 3; coronary artery bypass graft for ischemic heart disease in 2; com-

Table 1. Clinical characteristics of the warfarin and control groups

	Warfarin group (n = 41)	Control group (n = 323)	p value
Age, years	69.9 ± 12.1	66.0 ± 12.9	0.067
Male gender	29 (71)	177 (55)	0.053
Smoking	24 (59)	133 (41)	0.035
Drinking	16 (39)	138 (43)	0.652
Hypertension	36 (88)	293 (91)	0.572
Diabetes mellitus	9 (22)	81 (25)	0.662
Hypercholesterolemia	15 (37)	103 (32)	0.545
Hypocholesterolemia	1 (2)	12 (4)	0.999
Heart disease	26 (63)	38 (12)	<0.001
Liver disease	4 (10)	41 (13)	0.802
Previous ischemic stroke	28 (68)	23 (7)	<0.001
Previous ICH	5 (12)	36 (11)	0.795
SBP at admission, mm Hg	173 ± 28	183 ± 30	0.036
DBP at admission, mm Hg	88 ± 18	98 ± 17	<0.001
INR ≥2.0	25 (63)	0 (0)	<0.001
Blood glucose, mmol/l	7.8 ± 3.2	8.2 ± 3.5	0.506
NIHSS score at admission	13 (6–27)	13 (8–19)	0.729
Time interval to the first CT, h	2.1 (1.0–5.6)	1.8 (1.0–3.2)	0.081
Characteristics of hematoma			
Admission HV, cm^3	33.5 ± 55.3	21.1 ± 28.3	0.022
Multiple hematomas	9 (22)	49 (15)	0.264
Intraventricular bleeding	21 (51)	140 (43)	0.339
Putaminal hemorrhage	11 (27)	132 (41)	0.083
Thalamic hemorrhage	23 (56)	113 (35)	0.009
Lobar hemorrhage	7 (17)	41 (13)	0.435
Pontine hemorrhage	2 (5)	35 (11)	0.234
Cerebellar hemorrhage	2 (5)	8 (3)	0.376
mRS at 30 days or at discharge			
Length of hospital stay, days	28 (18–32)	23 (19–31)	0.162
mRS score ≥3	27 (66)	240 (74)	0.249
In-hospital mortality (mRS score = 6), %	24	9	0.003

Values are presented as numbers (percentage), mean ± SD, or median (interquartile range). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

plicated atheromatous lesions at the aortic arch in 2, and peripheral arterial disease in 1. Of the 41 patients, 28 had a history of brain infarction.

The following baseline characteristics were more common in the warfarin group than in the control group: smoking habit ($p = 0.035$); heart disease ($p < 0.001$); previous symptomatic ischemic stroke ($p < 0.001$), and admission INR ≥2.0 ($p < 0.001$). Admission systolic ($p = 0.036$) and diastolic ($p < 0.001$) blood pressures were lower in the warfarin group than in the control group (table 1).

HV on admission ($p = 0.022$) was larger in the warfarin group than in the control group. There were significantly more thalamic hemorrhages ($p = 0.009$) in the warfarin group than in the control group (table 1).

Although the frequency of a clinically poor outcome (mRS score ≥3) based on the mRS at 30 days or at discharge was not significantly different between the two groups, in-hospital mortality (mRS score of 6) was higher in the warfarin group than in the control group ($p = 0.003$; table 1).

Of the 364 patients, 3 had neurosurgery and 15 died before a second CT examination could be performed within 24 h. HE in the remaining 346 patients was examined. Both HV on admission ($p = 0.031$) and final HV ($p = 0.001$) were larger in the warfarin group than in the