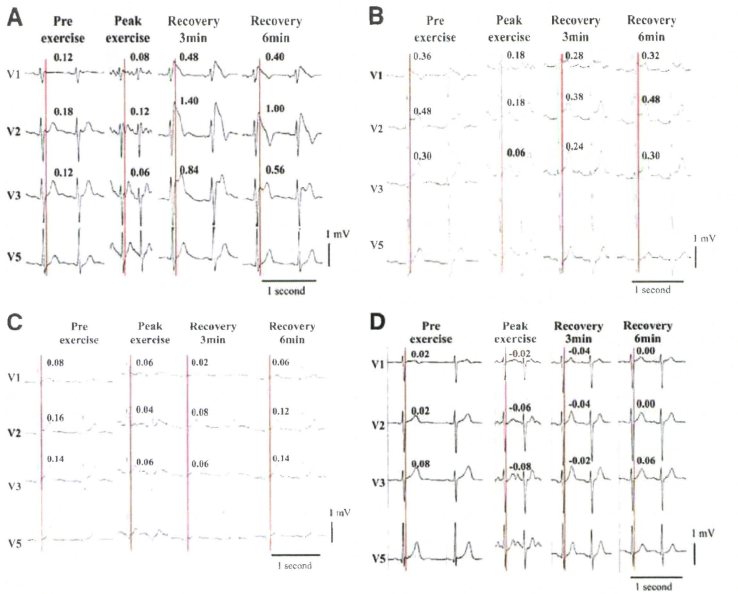

Figure 1 **Typical Responses of ST-Segment Amplitude in Leads V_1, V_2, V_3, and V_5 During Exercise Testing in Brugada Syndrome Patients**

(A) In the group 1 Brugada patient showing saddle-back type ST-segment (lead V_2) at baseline, ST-segment amplitude slightly decreased at peak exercise, but reascended at early recovery (3 min), resulting in typical coved-type ST-segment elevation. **(B, C)** In the group 2 Brugada patient and **(D)** in the control subject, ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline at recovery. It is noteworthy that the peak J-point amplitude in lead V_2 was augmented despite not showing ST-segment augmentation in **A** and **C**. The ST-segment amplitudes are shown as numeric values expressed in millivolts (mV). The **red vertical line** indicates the line from the end point of the QRS interval at electrocardiography lead V_5.

amplitude and ST40 amplitude decreased in most patients of both groups.

Comparison of HRR is shown in Figure 3. The HRR of group 1 patients was significantly larger than that of group 2 patients (32 ± 15 vs. 23 ± 10, p = 0.0007) and control subjects (32 ± 15 vs. 26 ± 10, p = 0.021). The differences of HRR between group 2 patients and control subjects were also statistically significant (23 ± 10 vs. 26 ± 10, p = 0.026).

Although there were no sustained or nonsustained ventricular arrhythmias throughout exercise testing, single premature ventricular complexes were observed during exercise in 8 of the group 1 patients and in 11 of the group 2 patients, and at recovery in 10 of the group 1 patients and in 9 of the group 2 patients. There were no significant differences between groups 1 and 2 in incidences of premature ventricular complexes.

Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics. Comparison of the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics between groups 1 and 2 patients are shown in Table 2. There were no significant differences in these characteristics between groups 1 and 2 except for the presence of *SCN5A* mutation and late potential (*SCN5A* mutation, 17% vs. 5%, p = 0.048; late potential, 82% vs. 53%, p = 0.004).

Follow-up. The mean follow-up period for the 93 BrS patients was 75.7 ± 38.4 months. During follow-up, 25 of all 93 BrS patients (27%) had cardiac events, and the incidence of cardiac events was significantly higher in group 1 than in group 2 patients (44% vs. 17%, p = 0.004). The period from exercise testing to cardiac events ranged from 1 to 78 months (median 12 months). One patient in group 2, who refused implantation of ICD and was taking disopyr-

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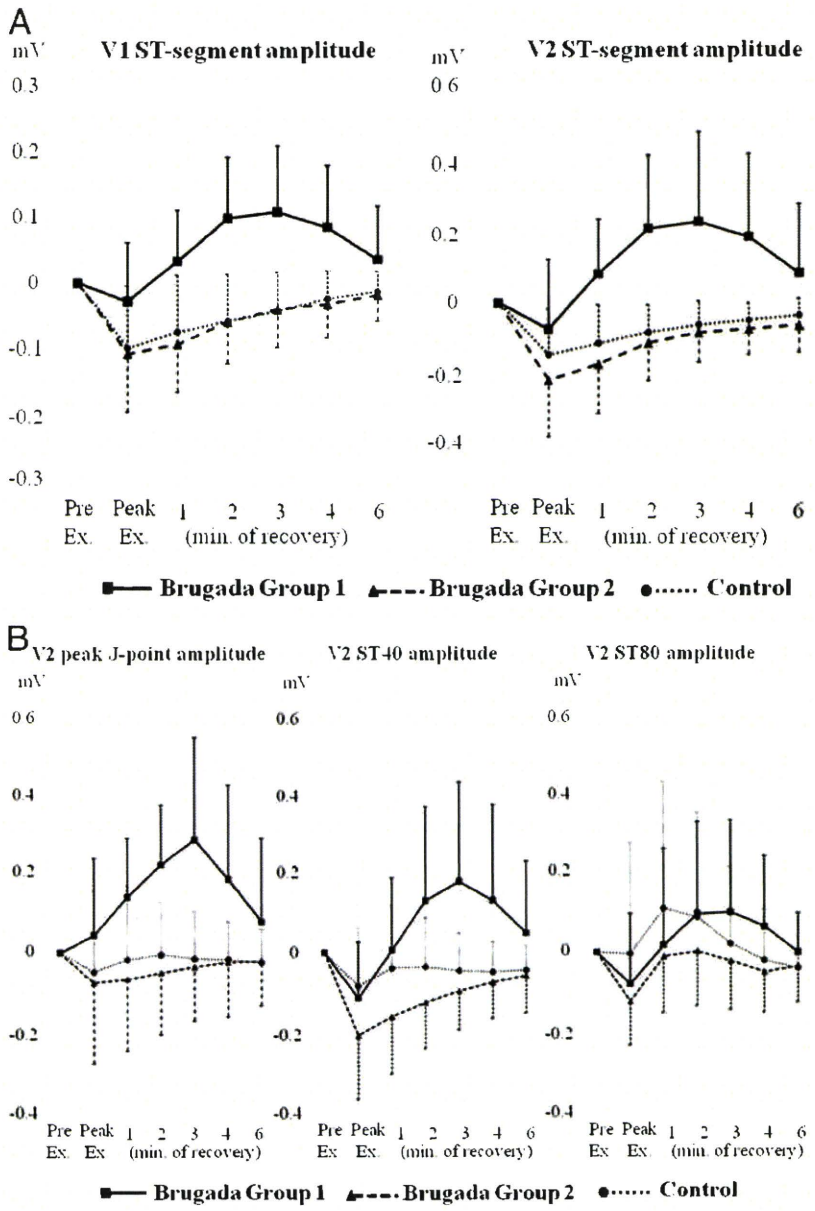

Figure 2 **Composite Data of Serial Changes of ST-Segment Amplitude**

(A) Composite data of serial changes of ST-segment amplitude in lead V_1 **(left)** and lead V_2 **(right)** during exercise (Ex.) testing in group 1 Brugada syndrome patients **(squares)** and group 2 Brugada syndrome patients **(triangles)**, and in control subjects **(circles)**. **(B)** Peak J-point amplitude **(left)**, ST40 amplitude **(middle)**, and ST80 amplitude **(right)** in lead V_2. The ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery in group 1 Brugada patients. In the group 2 Brugada patients and control subjects, the ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline level during recovery. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude. Since ST80 amplitude was influenced by T wave, especially at rapid heart rate, the trends of the 3 groups were somewhat different from ST-segment amplitude or ST40 amplitude. The ST-segment amplitudes are shown as values compared to pre-exercise ST-segment amplitudes. $p < 0.05$.

amide 300 mg daily, died of VF. Three of 7 patients with medication had cardiac events, including 1 death.

Predictors of outcome. Kaplan-Meier analysis demonstrated significant differences in the time to the first cardiac event depending on the presence of ST-segment augmentation during recovery from exercise (Fig. 4A). Group 1 patients had a significantly higher cardiac event rate than group 2 patients (log-rank, $p = 0.0029$). Previous history of VF (Fig. 4B) and positive *SCN5A* mutation (Fig. 4C) also had significant values for occurrence of subsequent cardiac events ($p = 0.0013$ and $p = 0.028$, respectively); however, spontaneous coved-type ST-segment elevation did not predict cardiac events ($p =$

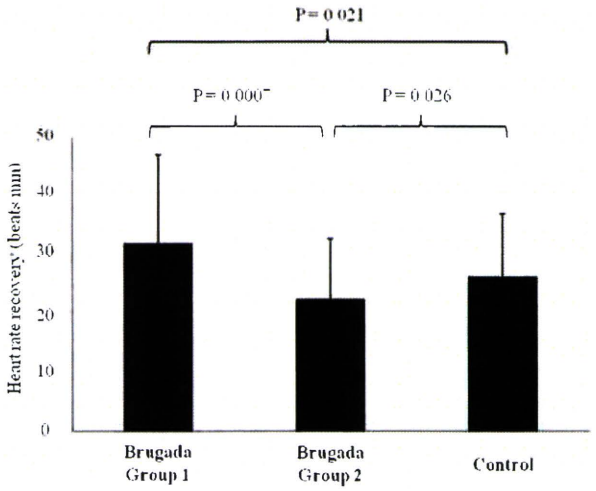

Figure 3 **Comparison of HRR After Exercise Cessation**

Comparison of heart rate recovery (HRR) 1 min after exercise cessation among Brugada syndrome patients of groups 1 and 2 and control subjects. The HRR in group 1 patients was significantly larger than that in group 2 (32 ± 15 beats/min vs. 23 ± 10 beats/min, p = 0.0007) and in control subjects (32 ± 15 beats/min vs. 26 ± 10 beats/min, p = 0.021). The differences of HRR between group 2 patients and control subjects were also significant (23 ± 10 beats/min vs. 26 ± 10 beats/min, p = 0.026).

0.068) (Fig. 4D). The results of Cox regression analysis are shown in Table 3. In univariate analysis, indexes predictive of cardiac events were previous episodes of VF (p = 0.003), ST-segment augmentation at early recovery (group 1; p = 0.005), and presence of *SCN5A* mutation (p = 0.037). In multivariate Cox regression analysis, previous episodes of VF and ST-segment augmentation at early recovery were significant and independent predictors of subsequent cardiac events (p = 0.005 and p = 0.007, respectively).

The incidence of cardiac events during follow-up in the subgroups according to symptoms before exercise testing is shown in Table 4. In the subgroup of 35 BrS patients with syncope alone, group 1 had a significantly higher cardiac event rate than group 2 (log-rank, 6 of 12 [50%] vs. 3 of 23 [13%], p = 0.016). Of note, among 36 asymptomatic patients, only 3 patients (9%) in group 1 experienced cardiac events. The log-rank test also demonstrated higher cardiac event risk in group 1 compared with group 2 (3 of 15 [20%] vs. 0 of 21 [0%], p = 0.039).

Discussion

The major findings of the present study were the following: 1) 37% of BrS patients showed ST-segment augmentation at early recovery during exercise testing; 2) ST-segment augmentation at early recovery was specific in BrS patients, and was significantly associated with a higher cardiac event rate, notably for patients with previous episode of syncope or for asymptomatic patients; and 3) BrS patients with ST-segment augmentation at early recovery showed significantly larger HRR. This is the first systematic report on the relationship between ST-segment augmentation during recovery from exercise and prognosis for BrS patients.

Augmentation of ST-segment elevation and possible mechanism. It is well known that autonomic function influences an extent of ST-segment elevation in BrS (8). The ST-segment elevation is mitigated by administration of β-adrenergic agonists and is enhanced by parasympathetic agonists such as acetylcholine in experimental and clinical investigations (5,14–16). Parasympathetic reactivation is thought to occur at early recovery after treadmill exercise testing, especially in the first minute after cessation of exercise (10,17). In the present study, we measured the ST-segment amplitude as a repolarization parameter rather than a depolarization parameter, and evaluated HRR to investigate the correlation between ST-segment augmentation and parasympathetic activity (9,18). The BrS patients who had ST-segment augmentation had significantly larger HRR compared with patients who did not, suggesting that the ST-segment augmentation was closely related to higher parasympathetic activity. However, it is still unclear whether ST-segment augmentation observed in the 34 BrS patients was simply due to more increased parasympathetic activity or to more increased susceptibility (hypersensitivity) to the parasympathetic reactivation.

Conversely, the *SCN5A* mutation was more frequently identified in group 1. Scornik et al. (19) reported that *SCN5A* mutation can accentuate parasympathetic activity toward the heart directly. It was also reported that specific mutations in the *SCN5A* gene may lead to augmentation of J-point amplitude or ST-segment amplitude during beta-adrenergic stimulation (20,21). Veldkamp et al. (20) demonstrated that a specific *SCN5A* mutation, 1795insD, augments slow inactivation, and delays recovery of sodium channel availability, thus reducing the sodium current and resulting in augmented peak J-point amplitude at rapid heart rate. Increased body temperature induced by exercise can be a risk of life-threatening arrhythmias in patients with BrS (22). A specific *SCN5A* missense mutation, T1620M, was reported to cause a faster decay of the sodium channel but slower recovery from inactivation, resulting in increased ST-segment elevation in precordial leads at higher temperatures during exercise. Although Amin et al. (13) reported that exercise induced augmentation of peak J-point amplitude, a depolarization parameter or at least combined parameter of both depolarization and repolarization, in all subjects tested, the incidence of increase in the peak J-point amplitude at peak exercise was lower (37%) in our Brugada patients. This is probably in part because only 9 (10%) of our 93 BrS patients had the *SCN5A* mutation. We could not identify significant differences in HRR, QRS duration, peak J-point amplitude (lead V_2), and ST-segment amplitude (leads V_1, V_2, V_3) at peak exercise between patients with and without *SCN5A* mutation (not shown), and that may be also due to the small number of BrS patients with *SCN5A* mutation.

Risk stratification in BrS. Implantation of an ICD is a first line of therapy for secondary prevention in patients with BrS who exhibited previous history of VF. The American College

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Table 2 Clinical, Laboratory, Electrocardiographic, and Electrophysiologic Characteristics and Long-Term Follow-Up of Groups 1 and 2 Brugada Syndrome Patients

Characteristic	Group 1 (n = 34)	Group 2 (n = 59)	p Value
Clinical characteristics			
Age at exercise testing, yrs	42 ± 11	48 ± 15	NS
Men	34 (100%)	57 (97%)	NS
Family history of SCD at age <45 yrs or Brugada syndrome	7 (21%)	16 (27%)	NS
Documented AF	7 (21%)	12 (20%)	NS
Documented VF before exercise testing	7 (21%)	15 (25%)	NS
Syncope alone before exercise testing	12 (35%)	23 (39%)	NS
Asymptomatic before exercise testing	15 (44%)	21 (36%)	NS
Age at first cardiac event, yrs	42 ± 13	45 ± 15	NS
ICD implantation	25 (74%)	38 (64%)	NS
Laboratory characteristics			
SCN5A mutation	6 (17%)	3 (5%)	0.048
Electrocardiographic characteristics			
RR, ms	951 ± 170	953 ± 140	NS
PR, ms	184 ± 28	175 ± 31	NS
QRS, ms	98 ± 14	98 ± 17	NS
QTc, ms	418 ± 46	415 ± 43	NS
ST-segment amplitude (mV) at baseline			
V_1	0.14 ± 0.09	0.16 ± 0.12	NS
V_2	0.41 ± 0.22	0.38 ± 0.26	NS
V_3	0.22 ± 0.13	0.19 ± 0.14	NS
Spontaneous coved-type ST-segment elevation in right precordial leads	30 (88%)	43 (73%)	NS
Signal-averaged electrocardiogram			
TfQRS, ms	122 ± 15	118 ± 17	NS
Late potential	28/34 (82%)	30/57 (53%)	0.004
Premature ventricular complexes during exercise	8 (24%)	11 (19%)	NS
Premature ventricular complexes at recovery	10 (29%)	9 (15%)	NS
Electrophysiologic characteristics			
AH interval, ms	107 ± 24	98 ± 27	NS
HV interval, ms	45 ± 8	44 ± 11	NS
Induction of VF	26/31 (84%)	33/47 (70%)	NS
Follow-up			
Cardiac events	15 (44%)	10 (17%)	0.004
Follow-up period, months	74.1 ± 42.2	76.5 ± 36.4	NS

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; TfQRS = total filtered QRS duration; VF = ventricular fibrillation; other abbreviations as in Table 1.

of Cardiology/American Heart Association/Heart Rhythm Society guidelines refer to BrS patients who have had syncope as having Class IIa indication for ICD therapy (23). However, there is still much room for argument with respect to treatments for patients who have had only syncope, and for asymptomatic patients (24–28). Although inducibility of VF during EPS (25,26), family history of SCD (24), spontaneous type 1 ECG (25,27), and late potential (28) have been proposed as predictors of cardiac events, the availability of these indexes remains controversial (7,29).

In the present study, a previous episode of VF (or aborted cardiac arrest) was the strongest predictor of subsequent cardiac events, as in previous studies (7,30,31). Moreover, ST-segment augmentation at early recovery during exercise testing was a significant and independent predictor of subsequent cardiac events in the present study. The results suggested that parasympathetic activity plays an important role in both ST-segment augmentation and subsequent cardiac events. As previously noted, it remains unclear that the cause of ST-segment augmentation in our 34 patients was a result of more increased parasympathetic activity or of more increased susceptibility of the patients to the increased parasympathetic reactivation.

Study limitations. First, BrS patients were confined to those who were hospitalized in our hospital for close investigation. That indicates these patients can be biased toward relatively high risk. Second, the present study is based on data from a small population of 93 patients; hence, it was not sufficient to evaluate the prognosis, and there also was a small number of events. Although we adopted a step-wise approach, the limited number of events can lessen the precision of the consequences for multivariate Cox regression analysis.

Conclusions

The presence of *SCN5A* mutation was a significant predictor of subsequent cardiac events by univariate Cox regression analysis. However, multivariate Cox regression analysis showed it was not a significant predictor of prognosis.

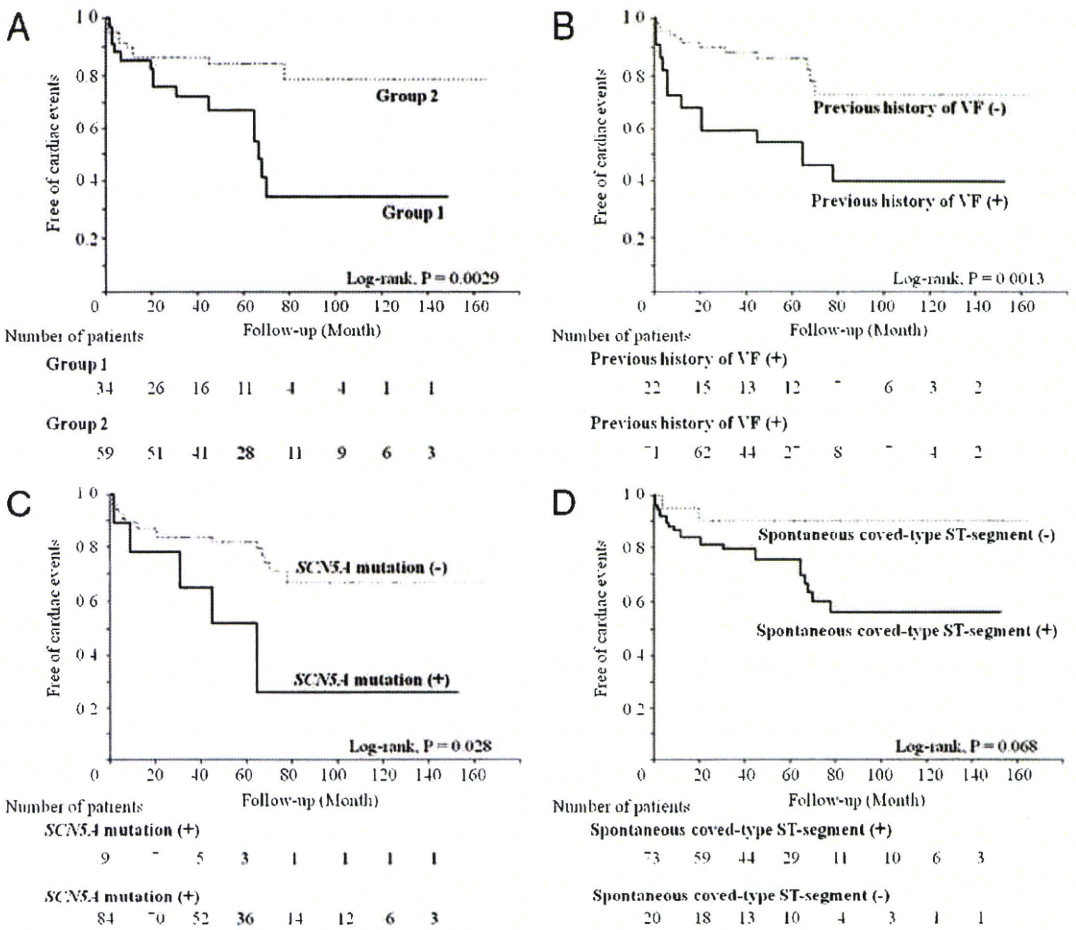

Figure 4 **Kaplan-Meier Analysis of Cardiac Events During Follow-Up**

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.

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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.

Subtraction Magnetocardiogram for Detecting Coronary Heart Disease

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Background: A large-scale magnetocardiogram (MCG) database was produced, and standard MCG waveforms of healthy patients were calculated by using this database. It was clarified that the standard MCG waveforms are formed with the same shape and current distribution in healthy patients. A new subtraction method for detecting abnormal ST-T waveforms in coronary heart disease (CHD) patients by using the standard MCG waveform was developed.

Methods: We used MCGs of 56 CHD patients (63 ± 3 years old) and 101 age-matched normal control patients (65 ± 5 years old). To construct a subtracted ST-T waveform, we used standard MCG waveforms produced from 464 normal MCGs (male: 268, female: 196). The standard MCG waveforms were subtracted from each subject's measured MCGs, which were shortened or lengthened and normalized to adjust to the data length and magnitude of the standard waveform. We evaluated the maximum amplitude and maximum current-arrow magnitude of the subtracted ST-T waveform.

Results: The maximum magnetic field, maximum magnitude of current arrows, and maximum magnitude of total current vector increased according to the number of coronary artery lesions. The sensitivity and specificity of detecting CHD and normal control patients were 74.6% and 84.1%, respectively.

Conclusions: The subtraction MCG method can be used to detect CHD with high accuracy, namely, sensitivity of 74.6% and specificity of 84.1% (in the case of maximum amplitude of total current vector). Furthermore, the subtraction MCG magnitude and its current distribution can reflect the expanse of the ischemic lesion area and the progress from ischemia to myocardial infarction.

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magnetocardiogram; subtraction; current-arrow map; Coronary Heart Disease

INTRODUCTION

Coronary heart disease (CHD) is the most common cause of death in the world. Advances in noninvasive coronary-artery imaging, such as x-ray coronary angiography[1] and multidetector computed tomography (CT),[1,2] has enabled early and precise detection of CHD. These tools are needed to treat artery constriction and improve the symptoms of angina. On the other hand, as functional tests of myocardial activity, exercise electrocardiogram (ECG) and single-photon-emission computed tomography (SPECT) are widely used for detecting signs of cardiac sudden death in CHD patients.[3,4] However, the distribution of myocardial electrical currents, which include information on damaged tissues, cannot be detected with these cardiac tests.

Noncontact magnetocardiograms (MCGs) can produce a myocardial-current-distribution map by detecting weak magnetic fields generated by myocardial electrical currents. The morphology of MCG waveforms produced from electrical currents is similar for each person because the MCG signals are less affected by organ conductivity, and the

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two-dimensional currents in the heart only produce a magnetic field. Given those facts, we constructed a database of 464 adult healthy patients[5] and a template MCG waveform.[6] In particular, the database and template enable the normal activity in the ST-T wave to be subtracted because of calm repolarization. Furthermore, some researchers have reported high CHD detection sensitivity[7–15] when MCGs are used because the ST-T MCG waves of CHD patients have an abnormal pattern. And MCGs are useful in detecting myocardial infarction (MI) in non-ST-segment elevation.[14,15]

To detect ST-T abnormality in CHD patients, we used our MCG-waveform template to construct a subtraction ST-T waveform. Subtraction of ST-T waveforms of CHD patients and control patients is used to evaluate the efficacy of detecting CHD, the difference between electrical current abnormalities in lesion areas, and the difference between ischemia and MI.

METHODS

Participants

Fifty-six Japanese CHD patients (10 females and 46 males) and 101 Japanese normal control patients (31 females and 70 males) participated, as listed in Table 1. This population is the same as that of our previous study,[16] which clarified CHD patients' spatial current abnormalities defined as a vessel-lesion diameter of >75%. The CHD patientswith two or three coronary-vessel lesions were defined as those with two lesions or three vessel lesions with diameters of ≥75%. We obtained informed consent from all participants and received approval from relevant ethical committees. Moreover, the CHD patients were classified into two groups, namely, ischemic (n = 12) or MI (n = 12), to evaluate the detection performance for ischemia, and patients with both ischemic and infarct areas were excluded. The ischemia and MI patients could be categorized as a minor part of the CHD patients because these patients were examined by SPECT.

MCG Recordings and Setup

MCG recording was performed above the chest of each participant for 30 seconds. The MCG signals were detected with a 64-channel MCG system (Hitachi High-Technologies Ltd., Tokyo, Japan)[17] in a magnetically shielded room. The detected MCG signals were passed through an analog band-pass filter (0.1–100 Hz) and an analog notch filter (50 Hz). The signals were then digitized at a sampling rate of 1 kHz by using an analog-digital converter. To remove the noise in the signals, the MCG data were averaged 20–30 times by using an ECG signal trigger. The MCG data were measured at three hospitals (Hitachi General Hospital, the National Cardiovascular Center, and University of Tsukuba Hospital) by using the same MCG system with the same sensitivity.

Table 1. Numbers of CHD and Control Patients

	N (n = 101)	CHD (n = 56)
Age (years)	63 ± 3	65 ± 6
Gender		
Female/Male	31 / 70	10 / 46
BMI	23.7	24.0
HR	63	63
SVD		25
LAD		16 (P:6, M: 5, D: 0, U: 5)
LCX		3 (P:1, M: 0, D: 1, U: 1)
RCA		6 (P:1, M: 2, D: 2, U: 1)
DVD		12
		LAD + LCX: 6
		LAD + RCA: 4
		LCX + RCA: 2
TVD		19

CHD = coronary heart disease, coronary artery lesion (> 75%); D = distal coronary artery; DVD = double vessel disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; M = middle coronary artery; N = age-matched normal controls with no history of cardiovascular disease and normal electrocardiogram (ECG) at rest; P = proximal coronary artery; RCA = right coronary artery; SVD = single vessel disease; TVD = triple vessel disease; U = unknown precise location.

Production of Subtracted MCG Waveforms

We focused on the ST-T segment in the MCG waveforms because previous studies reported that electrical current abnormality in CHD patients appears during ventricular repolarization in MCGs.[7–15] The T end of each patient was manually defined by using overlapped MCG waveforms.[5]

A subtracted ST-T waveform was calculated by subtracting the standard MCG waveform, which was produced by averaging the 464 normal control patients' MCGs,[6] from the measured MCG waveforms on each channel. Figure 1 shows the procedure for subtracting the ST-T waveforms. The time

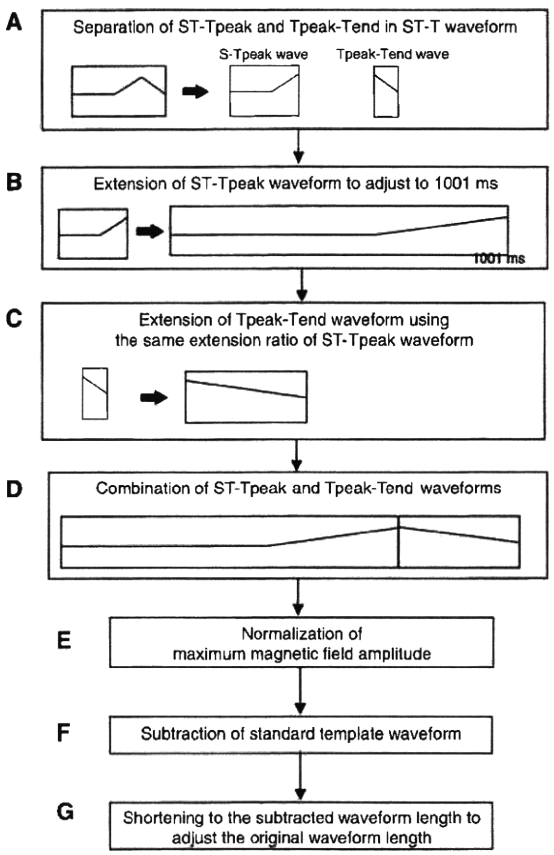

Figure 1. Procedure of subtracting ST-T waveform.

at which the amplitude of the ST-T waveform is a maximum varied among participants. The ST-T waveforms are, therefore, first separated into two parts, namely, an ST-Tpeak and a Tpeak-Tend, as shown in Figure 1A. Second, the ST-Tpeak waveforms are extended to 1001 milliseconds (Fig. 1B) by using the ratio of the duration of the ST-Tpeak waveform to the extended waveform. Third, the Tpeak-Tend waveforms are extended to 1001 milliseconds by using the same ratio for each participant (Fig. 1C).

In the next step, the ST-Tpeak and Tpeak-Tend waveforms are combined (Fig. 1D). The time interval of the data is lengthened by adding data points with zero amplitude after the Tend, and the amplitude of the magnetic field of both the Tpeak and Tpeak-Tend waveforms is normalized (Fig. 1E). The standard template waveform is then subtracted from the normalized ST-T waveforms (Fig. 1F). Finally, the time interval of the subtracted ST-T-waveforms is shortened to fit the original time interval (Fig. 1G). The subtracted ST-T MCG waveforms for each participant were obtained by this procedure.

Evaluation Method for Subtracting Waveforms

MCG parameters, which can be produced from the amplitude of the magnetic field and current distribution, are used to quantitatively evaluate the residual MCG signals in the subtracted ST-T waveforms. To investigate the current distribution, a current-arrow map (CAM) is used to indicate current vectors in the heart. The CAM indicates pseudo currents (Ix and Iy) defined by the derivatives of the normal component (Bz) of the MCG signals as

$$I_{x,n} = \frac{dB_{z,n}}{dy} \tag{1}$$

and

$$I_{y,n} = -\frac{dB_{z,n}}{dx}. \tag{2}$$

The magnitude of the current arrows ($I_{x,y} = \sqrt{(I_{x,n})^2 + (I_{y,n})^2}$) is plotted as a contour map, where n indicates channel number. The CAM helps in interpreting spatial heart electrical activity, and it can visualize the residual current component.

The above-mentioned CAM and the amplitude of the magnetic field at the Tpeak are used to calculate the following five parameters (three magnitude parameters and two two-dimensional distribution parameters).

1. Absolute value of the maximum amplitude of all MCG signals.
2. Absolute value of the maximum vector amplitude of all current vectors.
3. Maximum amplitude of total current vector (TCV).

The TCV[5,18] is obtained by summing all current arrows. The TCV ($\mathbf{I}$) of all current arrows can be calculated as a vector value by using the current arrow ($\mathbf{I_n}$) at each sensor,

$$\mathrm{I} = \sum_{n=1}^{64} \mathrm{I_n}(T), \tag{3}$$

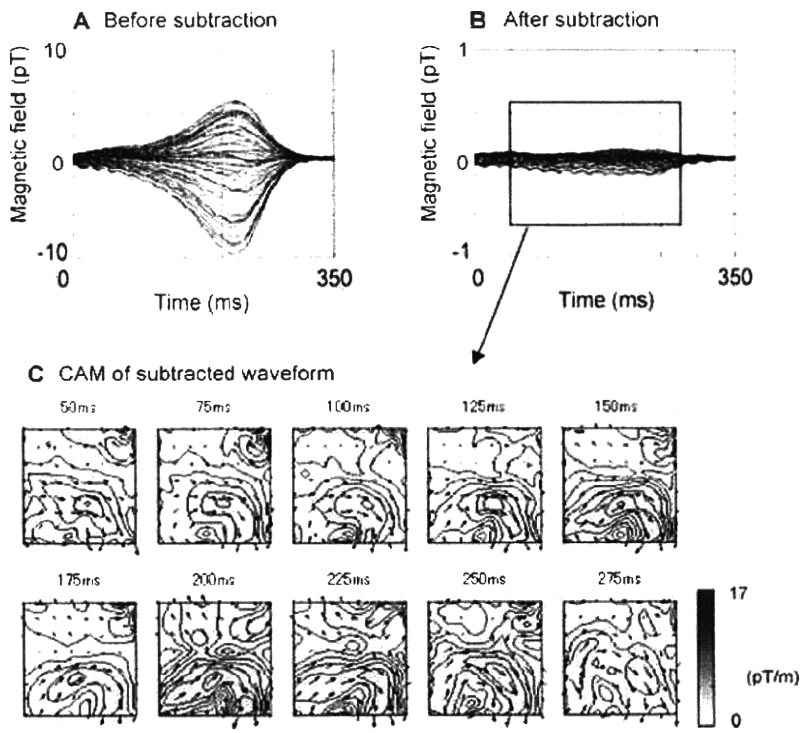

Figure 2. Subtracted ST-T waveform and current-arrow map (CAM) of typical normal control. (A) Original ST-T waveform. (B) Subtracted ST-T waveform. (C) CAM of (B).

where T is the calculated time. The TCV amplitude of the subtracted waveform is used because TCV has high sensitivity for detecting CHD.

4. Area ratio of abnormal current vector appearance.

Average (A) and standard deviation (σ) of the maximum current vector derived from step 2 in all healthy control patients were calculated in order to evaluate the abnormal current area. The number of current vectors with abnormal values above $A + \sigma$ is counted, and the number of abnormal current vectors is divided by total channel number, 64. The result of this division (given as a percentage) is used as the ratio of the areas where abnormal current vectors appear in the participant and control patients, hereafter referred to as the "area ratio of abnormal-current-vector appearance." For example, 100% indicates that all channels have abnormal values ($> A + \sigma$), and 25% indicates that 16 channels have abnormal values ($> A + \sigma$).

5. Two-dimensional frequency distribution of abnormal-current appearance

In the same manner as step 4, the number of appearances of abnormal-current vectors above $A + \sigma$ on each channel for each lesion group of CHD patients count is counted. The number (given as a percentage) is divided by the total number of participants in each lesion group. The number of appearances is plotted as a two-dimensional contour map of cumulative frequency. For instance, the 100% position in the two-dimensional contour map of three-vessel stenosis indicates that the 100% position always has an abnormal value ($> A + \sigma$). In this study, a two-dimensional contour map of each lesion group of the coronary artery was drawn.

RESULTS

Typical Subtracted ST-T waveform

A typical subtracted ST-T waveform and CAM of a healthy control is shown in Figure 2. While

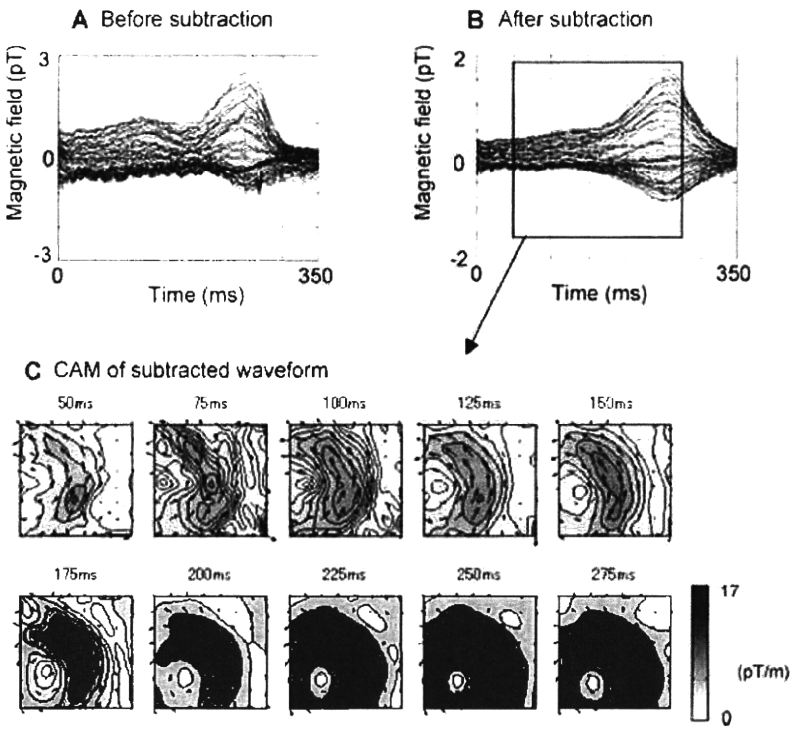

Figure 3. Subtracted ST-T waveform and current-arrow map (CAM) of typical CHD patient with triple vessel lesion. (A) Original ST-T waveform. (B) Subtracted ST-T waveform. (C) CAM of (B).

the amplitude of the ST-T waveform ranges from about −10 to 5 pT (Fig. 2A) before subtraction, the residual amplitude is very small (Fig. 2B) after subtraction, ranging from about −0.02 to 0.01 pT. In this case, up to 99.8% of the ST-T waveform can be removed. In the CAM in Figure 2C, the current vectors have small amplitude, and the residual currents are weaker than those before subtraction.

Figure 3 shows a typical subtracted ST-T waveform and the CAM of triple vessel disease (TVD) in CHD patients. The amplitude of the ST-T waveform ranges from about −1 to 2.5 pT (Fig. 3A) before the subtraction procedure, and the amplitude after the procedure is still high, ranging from about −0.9 to 1.8 pT. The reduction rate is about 23%. In the CAM in Figure 3C, a right upward current with high amplitude (about 24 pT/m) appears. This pattern, with large residual ST-T components, is found in almost all CHD patients.

Relationship between Parameters and Coronary-Artery Lesions

Figure 4 shows the maximum amplitude of the magnetic field, maximum current vector, maximum amplitude of the TCV, and area ratio of abnormal current vector appearance, which were calculated from the subtracted ST-T waveform and its CAM of the control and CHD patients. In the case of all parameters, the mean values increase with increasing number of coronary artery lesions. The difference between control and lesion parameters is significant ($P < 0.01$).

The sensitivity and specificity of the MCG for detecting CHD by using these four MCG parameters, listed in Table 2, were calculated. Criteria for each parameter are defined as the mean value plus the standard deviation for healthy control patients. In Table 2, the maximum amplitude of the TCV is highly sensitive (i.e., 74%) and has specificity of 84%, and the area ratio of abnormal current vector appearance has the highest specificity of 92.2%.

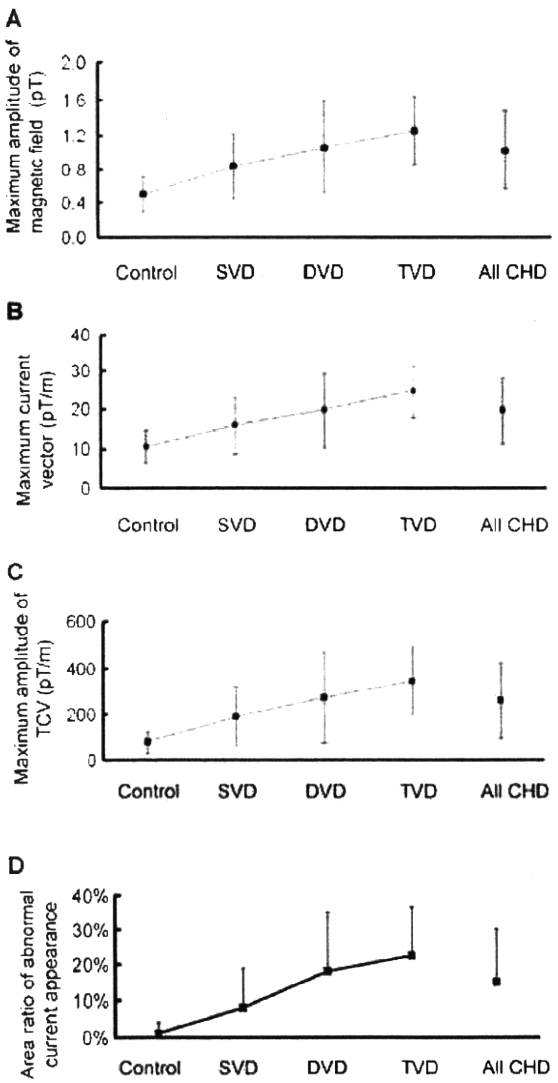

Figure 4. Relationship between each parameter and each lesion. (A) Maximum amplitude of magnetic field, (B) maximum current vector, (C) maximum amplitude of TCV, (D) area ratio of abnormal current vector appearance.

Two-dimensional frequency distribution of abnormal current vector appearance in each lesion patient is summarized in Figure 5. In the healthy control patients, there are no abnormalities in all measurement areas. In the left-anterior-descending (LAD) coronary artery of single-vessel-disease (SVD) patients, there is a 30% probability of abnormal current vector appearance near the septum and the left ventricular anterior wall. In the left-circumflex (LCX) coronary artery of SVD patients, there is a 50% probability throughout the left and right ventricular walls. In the right coronary artery (RCA) of SVD patients, there is a 30% probability near the septum and right ventricular wall. The 30% probability in the LAD and LCX coronary arteries of double-vessel-disease (DVD) patients is similar to that in the SVD-LAD artery, and the probability remains the same throughout the right ventricular wall and apex. In the LAD and RCA coronary arteries of DVD patients, there is 50% probability throughout the left ventricle wall to the septum and the top of the right ventricle. In the LCX and RCA coronary arteries of DVD patients, there is a high probability (90%) from the left ventricle upward. In patients with TVD, there is a 60% probability throughout the left and right ventricle walls.

Table 2. Summarized List of Sensitivity and Specificity of Each Parameter

	Sensitivity (%)	Specificity (%)
Maximum amplitude of magnetic field	67.2	86
Maximum current vector	67.3	84.5
Maximum amplitude of TCV	74.6	84.1
Area ratio of abnormal current vector appearance	60.0	92.2

TCV = total current vector.

Relationship between MI and Ischemic Groups

The four MCG parameters (maximum amplitude of magnetic field, maximum current vector, maximum amplitude of TCV, and area ratio of abnormal current vector appearance) for the MI and ischemic groups are plotted in Figure 6. These groups have much higher values for all parameters, and they significantly differ from those of the control patients ($P < 0.01$). Moreover, the values of all parameters of the MI group are higher than those of the ischemic group.

DISCUSSION

Advantages of the Subtraction Method

As for the subtraction method, the ST-T waveform is separated into two segments, namely, an

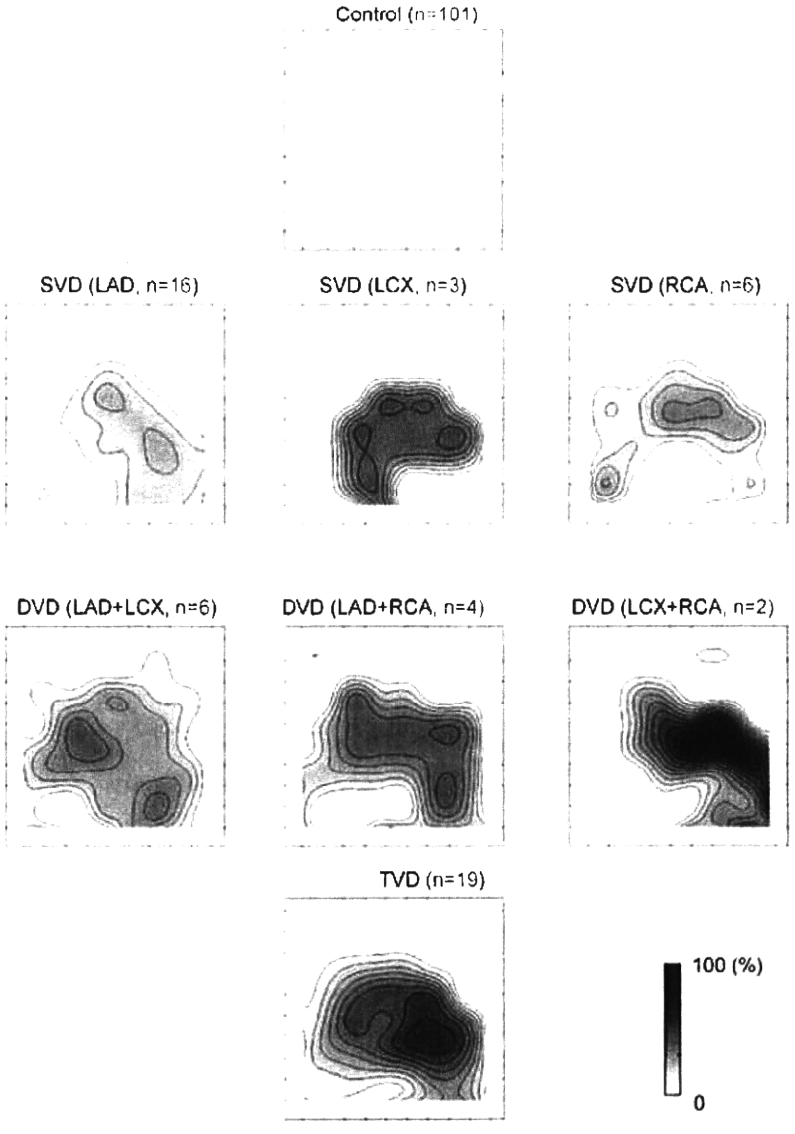

Figure 5. Two-dimensional frequency distribution of abnormal current appearance in each lesion patient and control.

ST-Tpeak and a Tpeak-Tend. To calibrate the Tpeak time for all subjects, the separation was necessary because the Tpeak time varied for each subject. If the Tpeak time is different for each subject, the template ST-T waveform (which is used in the subtraction method) will be an incomplete shape because the amplitude of the produced ST-T waveform is very small (due to the waveform-averaging process). The difference between the Tpeak time for each subject may be associated with the difference in the action potential duration of the epicardium of each patient.[19] The waveform separation, therefore, compensates the individual differences of Tpeak time, in contrast with the general averaging method for removing external signals such as maternal signals[20] and ventricular activity.[21]

After the separation, the ST-Tpeak segment was extended to 1001 milliseconds (1000 ± 1 milliseconds) to normalize the time duration. The last

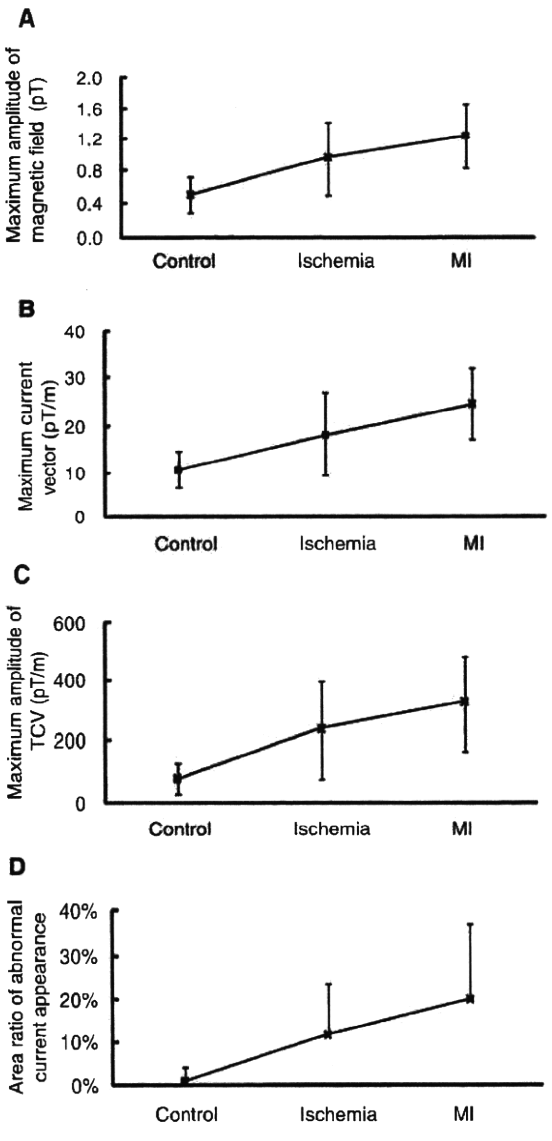

Figure 6. Relationships among control, ischemia, and myocardial infarction. (A) Maximum amplitude of magnetic field, (B) maximum current vector, (C) maximum amplitude of total current vector, (D) area ratio of abnormal current vector appearance.

time point, namely, the last 1 milliseconds in 1001 milliseconds, was used to superpose the normalized Tpeak-Tend waveform on the normalized ST-Tpeak waveform. On the other hand, 1000 milliseconds was chosen for easy calculation of the normalization ratio, and 1000 milliseconds must be sufficiently longer than a general ST-Tend time in order to obtain a positive normalization ratio. The authors, therefore, consider that 1000 milliseconds is adequate time for making the template waveform.

The subtracted ST-T peak of normal subjects is significantly decreased in Figure 2B, while that of a CHD patient (Fig. 3B) has a higher amplitude. The difference between the peaks indicates that a normal electrical-current vector with the same direction exists in the ventricular area. It is, therefore, considered that the subtracted waveforms of the CHD patients are produced by the abnormal residual currents (which indicate an ischemic area).

The increase in each MCG parameter in Figure 4 and the abnormal area in Figure 5, according to the increase in lesion sites, indicates that the increase in lesion areas enhances the residual electrical components or degrades normal electrical activities. The subtraction method is, therefore, helpful for estimating the lesion area easily.

On the other hand, a stenosis site in the coronary arteries was not found in the CAM of the subtracted waveform of each patient. This may be because the occupied area of each coronary artery becomes complementary in the ventricular muscle[22] and the individual variation of coronary-artery shape results in difficulties in identifying it.

Detection of Abnormalities in CHD Patients

Other groups have detected abnormalities in CHD patients by using magnetic field parameters (MFPs), which are calculated from the MCG data in the ventricular repolarization phase.[10,11] In particular, it has been reported that the four MFPs are the most sensitive indicators for diagnosing CHD patients,[10] and the detection sensitivity (86.4%) and specificity (82.5%) possible by using the MFPs is higher than our results (sensitivity: 74.6%; specificity: 84.1%). However, quoting the same patients' data, our previous report clarified the decrease in MFP sensitivity and specificity compared with the results obtained with our current-distribution parameters (CDPs).[16] We consider that CDP is the most important parameter for detecting CHD. Although the sensitivity and specificity obtained with CDPs are also high, the correlation between abnormal score and lesion area is not good. In this study, we assumed that abnormal current distribution depending on CHD is extracted by subtraction of normal electrical-current activities, and

we found a good correlation between the number of lesion sites and the magnitude of subtracted waveforms.

Furthermore, as for the subtraction MCG method, the highest values of MCG parameters of patients with MI areas, as shown in Figure 6, reflect the lack of electrical activation (depending on the infarction area). The difference between MI and ischemia, therefore, shows that ischemic status can be evaluated with this method. Consequently our proposed CHD-evaluation method using subtracted MCG ST-T waveforms makes it possible to estimate sizes of infarctions and coronary-artery lesions.

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LIMITATION OF THIS STUDY

This study has the following limitations. First, CHD patients were identified in terms of coronary artery stenosis only; therefore, the status such as ischemia, MI, and stable/unstable angina of all patients were not distinguished. Second, the subtraction method may be insufficient in the case of MI patients with a low-amplitude T wave whose T-wave peak cannot be identified because the subtraction method needs a correct T-wave peak as a reference point.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Clinical Effect of Implantable Cardioverter Defibrillator Replacements

– When Should You Resume Driving After an Implantable Cardioverter Defibrillator Replacement? –

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Background: The intervals of the driving restrictions after an implantable cardioverter defibrillator (ICD) replacement vary across the different countries around the world. However, little is known regarding the appropriate duration for driving restrictions after an ICD replacement. The aim of this study was to investigate the clinical effect of ICD replacements and to elucidate when to resume driving an automobile after an ICD replacement.

Methods and Results: The study reviewed 139 consecutive patients with an ICD replacement in order to evaluate the incidence of ICD therapies before and after ICD replacements, and to assess the time-dependence of the ICD therapies after the ICD replacement. There was no significant difference in the incidence of ICD therapies delivered during durations of 3 months and 6 months before and after the ICD replacement (P=0.28, and 1.0, respectively). ICD therapies after the replacements were observed in 8.6% of the patients who were legally eligible to drive according to the Japanese guidelines at 1 year, and that was associated with a relatively low annual risk of death or injury to others.

Conclusions: Implantable cardioverter defibrillator replacements did not affect the future ICD therapies under similar algorithms. The appropriate interval for driving restrictions after an ICD replacement is recommended to be a week or so, with a system integrity check performed before resumption of driving. (*Circ J* 2010; **74:** 2301–2307)

Key Words: Driving restriction; ICD therapy; Implantable cardioverter defibrillator; Replacement

An implantable cardioverter defibrillator (ICD) is an effective therapy for terminating ventricular arrhythmias and preventing sudden cardiac death.[1–3] However, patients with an ICD have an ongoing risk of sudden incapacitation, which might cause severe car accidents. Concerns about driving automobiles focus on the risk of symptomatic ventricular tachyarrhythmias and/or ICD therapy deliveries. Several studies have investigated the risk associated with driving in this population.[4–7] Based on these investigations, guidelines for driving restrictions in patients with an ICD have been published in many countries.[8–13] In cases of an ICD replacement only, without the replacement of the lead system, the patients are advised not to drive for 1–6 months in Japan.[12,13] In contrast, the consensus statement that was published recently from the European Heart Rhythm Association recommends driving restrictions of 1 week after an ICD replacement.[10] In the USA, although the duration of the driving restrictions after an ICD replacement was not mentioned specifically, patients without any ICD therapy deliveries for 6 months prior to the replacement may resume driving after they recover from the operation (within at least 1 week). One of the factors for these differences is in the lack of data related to the ICD therapies before and after the ICD replacement. As the number of patients with an ICD grows,[14] an increasing number of patients are undergoing ICD replacements. It is very important for clinicians and patients

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Table 1. Characteristics of the Patients With ICD Replacements (Excluding the Patients With Lead System Replacements)

No. of patients	128
Males (%)	100 (78)
Age at implantation (years)	54±14
Primary prevention (%)	38 (28)
Underlying disease (primary prevention)	
Brugada syndrome	42 (22)
Coronary artery disease	30 (5)
Hypertrophic cardiomyopathy	12 (3)
Idiopathic ventricular fibrillation	10 (0)
Dilated cardiomyopathy	8 (3)
Sarcoidosis	8 (0)
Other	18 (5)

ICD, implantable cardioverter defibrillator.

to determine an appropriate driving restriction period after an ICD replacement. We evaluated the incidence of ICD therapy deliveries before and after ICD replacements and assessed the time-dependence of the ICD therapies after the ICD replacement in order to recognize the annual risk of death or injury to others.

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Methods

Study Population

The records of 139 consecutive patients who received an ICD replacement from September 2004 to December 2008 at the National Cardiovascular Center in Osaka, Japan, were reviewed. Among the 139 patients that underwent a replacement of an ICD, 11 patients received a replacement or implantation of the lead system simultaneously. Most of the possible complications described following an implantation of an ICD are related to the lead system.[15–19] Having considered that fact, we excluded those 11 patients with the lead system replacements from this study.

The clinical characteristics of the patients who had an ICD replacement only are shown in Table 1. Regarding the ICD indications, 90 (72%) were for secondary prevention, whereas the remaining 38 (28%) were for primary prevention. The underlying pathology was Brugada syndrome in 42 (33%) patients, coronary artery disease in 30 (23%), and hypertrophic cardiomyopathy in 12 (9%). The indications for the ICD implantation generally adhered to the available evidence and guidelines over time. All the ICD implantations and replacements were performed by transvenous access and a fluoroscopy-guided endocardial lead placement. The devices were manufactured by Medtronic Inc (Minneapolis, MN, USA), the Guidant Corp (St. Paul, MN, USA), and St Jude Medical Inc (St. Paul, MN, USA), and were equipped with anti-tachycardia pacing as well as having direct current shock delivery features. The baseline programming of the device depended on the implanting or follow-up physicians. When replacing an ICD, we usually selected the ICD made by the same manufacturer as the previous one in order to avoid any major changes in the diagnostic algorithm, unless there was a particular reason not to do so. When inappropriate therapies occurred because of a manufacturer-specific algorithm and we were forced to replace their ICD with that from a different manufacturer, even if it had sufficient battery level. In such cases, the number of ICD therapies decreased after the replacement. Therefore, in this study, we excluded patients whose replacement ICD was manufactured by a different supplier due to the reasons described above.

Some patients had several ICD replacements. The earlier generation ICDs had immature functions for discriminating supraventricular tachycardia from ventricular tachycardia (VT), resulting in more inappropriate ICD therapies. For the purpose of this study, in those patients, we adopted the last ICD replacement in order to reflect the functions of the modern ICDs.

This investigation was approved by the institutional ethics committee.

Follow-up

All patients were followed up at the ICD clinics 1 month after the ICD replacement and then every 2–6 months thereafter. Device interrogations were performed at scheduled and event-driven visits. The baseline and follow-up data were entered prospectively in the ICD clinic database. The outcome was analyzed by using the data collected through regular clinic follow-up visits, emergent visits and hospitalizations. Additional data were collected from the ICD follow-up notes, office notes, and computer records. Information was collected on the demographics, past medical history, type of the ICD implant, and ICD interrogation results. All identified shocks were reviewed independently by 2 experienced clinical electrophysiologists in a blinded fashion. Appropriate shocks were defined as shocks delivered during ventricular fibrillation (VF)/VT. The incidence of syncope or loss of consciousness with inappropriate therapies was unknown and the drivers might be affected similarly by appropriate and inappropriate therapies. Considering these concerns, to calculate the cumulative rate of ICD therapies delivered after the replacement, the primary end-point was defined as either appropriate therapies (shocks or anti-tachycardia pacing) or other inappropriate therapies.

Statistical Analysis

Continuous variables were expressed as the group mean value±SD. Other data were presented as a percentage of the total. Kaplan-Meier survival analyses and log rank tests were used for end-points of any ICD therapies. McNemar's exact test was also used when we analyzed the incidence of the ICD therapies before and after the ICD replacement.

Results

Incidence of ICD Therapies Before and After ICD Replacement

In order to investigate the clinical effect of the ICD replacements on the ICD therapies, we performed a comparison of the incidence of ICD therapies before and after the replacements. In each comparison, we excluded the patients who had not been followed up for a specified period after the ICD replacement as censored cases. Among 128 patients who only had an ICD replacement, we excluded 13 patients as censored cases and investigated the remaining 115 patients. Regarding the duration of 3 months before and after the ICD replacement, no significant difference in the incidence of ICD therapies was observed (2/118 vs 6/118, respectively, P=0.28 using McNemar's exact test; Table 2). Eight patients experienced ICD therapies during the 6 months before the ICD

Table 2. Incidence of ICD Therapies During the 3 Months Before and After ICD Replacement

ICD therapies during the 3 months before the ICD replacement	ICD therapies during the 3 months after the ICD replacement		Total	Censored case
	Yes	No		
Yes	0	2	2	0
No	6	110	116	10
Total	6	112	118	10

ICD, implantable cardioverter defibrillator.
P=0.28 McNemar's exact test.

Table 3. Incidence of ICD Therapies During the 6 Months Before and After ICD Replacement

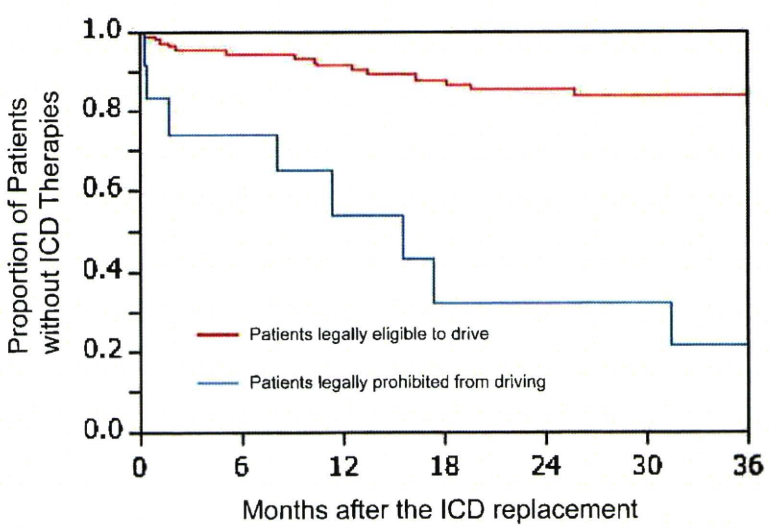
ICD therapies during the 6 months before the ICD replacement	ICD therapies during the 6 months after the ICD replacement		Total	Censored case
	Yes	No		
Yes	3	5	8	0
No	4	101	105	15
Total	7	106	113	15

ICD, implantable cardioverter defibrillator.
P=1.0 McNemar's exact test.

Table 4. Incidence of ICD Therapies 1 Year Before and After the ICD Replacement

ICD therapies 1 year before the ICD replacement	ICD therapies 1 year after the ICD replacement		Total	Censored case
	Yes	No		
Yes	4	4	8	2
No	7	85	92	26
Total	11	89	100	28

ICD, implantable cardioverter defibrillator.
P=0.56 McNemar's exact test.



No. of Patients							
Patients legally eligible to drive	115	99	86	70	58	46	26
Patients legally prohibited from driving	13	9	6	4	4	4	2

Figure 1. Cumulative probability of the incidence of implantable cardioverter defibrillator (ICD) therapy delivery in patients legally eligible to drive and in the patients legally prohibited from driving based on Japanese guidelines. There was a significant difference in the incidence of ICD therapies between the 2 groups (P<0.001).

Table 5. Characteristics of the ICD Therapies in Patients Legally Eligible to Drive and in Patients Legally Prohibited From Driving

	Patients legally eligible to drive	Patients legally prohibited from driving	Total
No. of patients	115	13	128
Follow-up period (years)	2.3±1.5	1.7±1.2	2.2±1.5
Incidence of ICD therapies	18	8	26
Appropriate ICD therapies	13	7	20
Inappropriate ICD therapies	5	1	6
Time to the first ICD therapy (months)	13.8±12.3	8.1±6.7	12.1±11.1

ICD, implantable cardioverter defibrillator.

Table 6. Proportion of Patients Who Experienced ICD Therapies After Replacement

	Proportion of patients who experienced ICD therapy after the ICD replacement		
	3 months	6 months	1 year
Incident-free period before the ICD replacement			
3 months	5.1% (6/116)	6.3% (7/111)	11.3% (11/97)
6 months	3.6% (4/111)	3.8% (4/105)	7.5% (7/93)
1 year	3.7% (4/107)	3.9% (4/102)	7.6% (7/92)

ICD, implantable cardioverter defibrillator.
Some cases were omitted because they were censored cases.

replacement. In contrast, during the 6 months after the replacement, ICD therapies were observed in 7 patients, of which 4 patients had not received any prior to the replacement. This difference was not statistically significant (P=1.0 using McNemar's exact test; Table 3). In 1 patient who did not have ICD therapy during the 6 months before the replacement, ICD therapies after the replacement were related to that replacement, as discussed in detail below. A comparison of the frequency of ICD therapy 1 year before and after the replacement yielded the same results (11/100 vs 8/100, respectively, P=0.56 using McNemar's exact test; Table 4).

Time-Dependence of ICD Therapies After ICD Replacements

According to the Japanese guidelines for driving restrictions in patients with an ICD, we divided the study population into 2 groups: the patients legally eligible to drive and those legally prohibited from driving.[12,13] The patients legally eligible to drive were defined as the subjects in whom 6 months had passed since the ICD implantation and who did not have any ICD therapies in the last 12 months before the replacement. This means that once patients have an ICD implantation, they have to refrain from driving for at least 6 months. They can then resume driving if they have not experienced any therapy for the 6-month period. After any ICD therapy, a 1-year suspension will be given. Figure 1 shows the cumulative probability of the incidence of an ICD therapy delivery in the patients legally eligible to drive and in the patients legally prohibited from driving. As demonstrated, there was a significant difference in the incidence of ICD therapies between the 2 groups (P<0.001). The incidence of ICD therapies, including both appropriate and inappropriate therapies, occurred in 5.5% of the patients legally eligible to drive at 6 months, 8.6% at 1 year, and 14.6% at 2 years, while it was found in 25.9% of the patients legally prohibited from driving at 6 months, 45.9% at 1 year and 67.5% at 2 years. Table 5 indicates the characteristics of the ICD therapies in the 2 groups. During a mean follow-up period of 2.3 years, 13 patients legally eligible to drive experienced appropriate ICD therapies and 5 had inappropriate ICD therapies.

Table 6 demonstrates the proportion of patients who experienced ICD therapies after the replacement in each incident-free period before the replacement. As is obvious from the table, the longer incident-free period resulted in the lower probability of ICD therapy after the replacement. Even in patients with a 3-month incident-free period before the ICD replacement, the annual incidence of ICD therapy was 11.3%.

A Case of an Inappropriate Therapy Related to a Change in the Algorithm

In our cohort of 128 patients, 1 patient experienced an inappropriate therapy related to a change in the algorithm. Before the ICD replacement, this patient had never experienced any inappropriate therapies due to sinus tachycardia. The previous ICD was removed and a new-generation GEM series ICD (GEMIIDR; Medtronic Inc) was implanted without any complications. Ten days after the ICD replacement (1 day after discharge), an ATP therapy was delivered for sinus tachycardia. We concluded that the reason for the inappropriate therapy was the result of the elimination of the onset criterion for sinus tachycardia. This onset criterion was installed in the previous ICD and worked efficiently.

Discussion

Assessment of the Risk During Driving

Recommendations for the resumption of driving after an ICD replacement vary among the countries. Several guidelines have reviewed this problem. A recent consensus statement from the European Society of Cardiology[10] made a distinction between private driving and professional driving, because of the high risk of fatal accidents involving professional drivers. For private drivers, the task force recommended a restriction of 1 week when an ICD was replaced. In the case of a replacement of the ICD and lead system or lead system alone, a driving restriction of 4 weeks was recommended, with a system integrity check before the resumption of driving. In

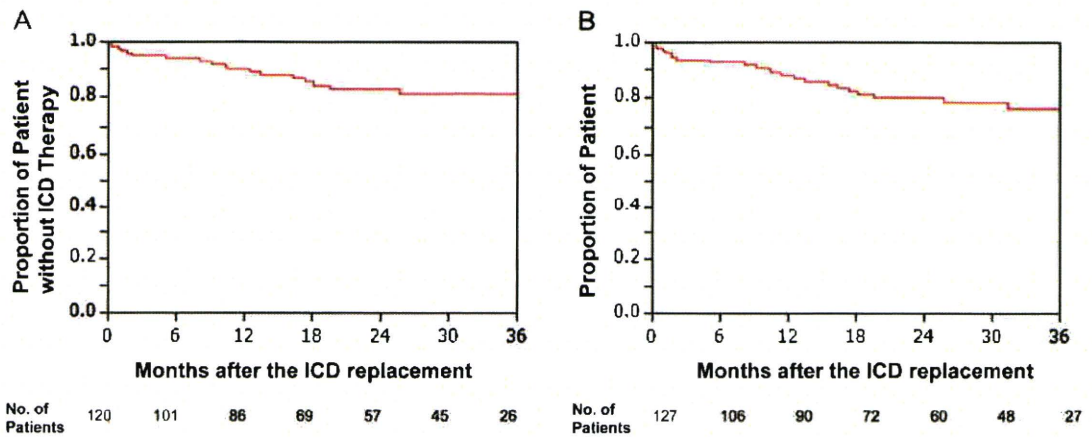


Figure 2. Cumulative probability of the incidence of implantable cardioverter defibrillator (ICD) therapies in patients legally eligible to drive based on guidelines from the USA and the European Heart Rhythm Association. (**A**) Only 10.1% of legally eligible to drive patients were supposed to have ICD therapies during the first year after the ICD replacement, based on guidelines from the USA. (**B**) 12.2% of the legally eligible to drive patients were supposed to experience an ICD therapy during the first year after the ICD replacement, based on guidelines from the European Heart Rhythm Association.

the statement, they used *the Risk of Harm (RH) formula (RH=TD×V×SCI×Ac)*,[11] where TD is the proportion of time spent behind the wheel or distance driven in a given time period; V is the type of vehicle driven; SCI is the yearly risk of sudden cardiac incapacitation; and Ac is the probability that such an event will result in a fatal or injury producing accident.

According to the guidelines of the Canadian Cardiovascular Society, the Canadian Council of Motor transport[11] and the consensus statement published by the European Society of Cardiology,[10] the private automobile driver with a 0.22 or lower risk of sustaining an SCI should be allowed to drive. We applied this criterion in our analysis. In Japan, patients undergoing ICD implantations are not allowed to drive for 1–6 months.[12,13] If an ICD therapy occurs after the implantation, either with or without an associated syncope or presyncope, patients should be advised not to drive for the next entire year. Therefore, legally eligible drivers after an ICD replacement are those patients in which 6 months has passed since the ICD implantation and who have not had any ICD therapies in the last 12 months. In our cohort study, only 8.6% of the patients legally eligible to drive experienced an ICD therapy during the first year after the ICD replacement. Even if all the ICD therapies lead to an SCI, this level of yearly risk of ICD therapies is considered to be within a socially acceptable level.

Some studies investigated the occurrence of ICD therapy, syncope, and behavioral incapacitation in ICD patients during driving.[4,6,7] A low rate of accidents has been noted in these studies. Also, the AVID trial evaluated 627 patients who completed a questionnaire a median of nine months after entry into the trial.[7] Syncope, dizziness or palpitations necessitating stopping the vehicle and ICD shock occurred in 2, 11 and 22 percent, respectively. However, accidents preceded by symptoms suggested an arrhythmia in 0.4%. Despite the low probability of a motor vehicle accident preceded by symptoms associated with arrhythmia, symptoms that could result in sudden incapacitation occurred relatively frequently. These data from previous reports suggest that the annual risk of harm to other drivers and passersby by drivers with an ICD might be lower than the occurrence of arrhythmic symptoms that could result in sudden incapacitation.

Application of the Guidelines From the USA and Europe

According to the Recommendations from the American Heart Association and Heart Rhythm Society,[8] patients without any ICD therapies within 6 months prior to the replacement can resume driving in the USA. Although the laws vary within the USA, most experts recommend patients to refrain from driving for approximately 1 week after the replacement. Although the replacement of an ICD is a simple operation, a short period of driving restrictions should be imposed because this is the accepted way with ICD implantations. We analyzed our data based on this guideline from the USA. As shown in **Figure 2A**, only 10.1% of the patients legally eligible to drive, based on the recommendations in the USA, are supposed to have ICD therapies during the first year after the ICD replacement. Even that frequency of ICD therapies could still be considered permissible. A recent statement from the European Heart Rhythm Association presented a permissive attitude toward patients with ICDs. Basically, after an ICD replacement, the patients are allowed to drive if they have not had any appropriate ICD therapies within the last 3 months. Even when applying this statement to our cohort (**Figure 2B**), 12.2% of the patients legally eligible to drive, based on the European Heart Rhythm Association recommendations are supposed to experience ICD therapy during the first year after the ICD replacement. The rate of ICD therapies was relatively low and within an acceptable level. Given this perspective, the current recommendations from the USA and Europe are considered to be acceptable.

Appropriate Interval for Driving Restrictions After an ICD Replacement

We also evaluated the clinical effect of the ICD replacement on the incidence of ICD therapies. During an ICD replacement procedure, the pocket is opened, the lead is disconnected from the ICD, and a new one is connected after assuring the