

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

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.

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.

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

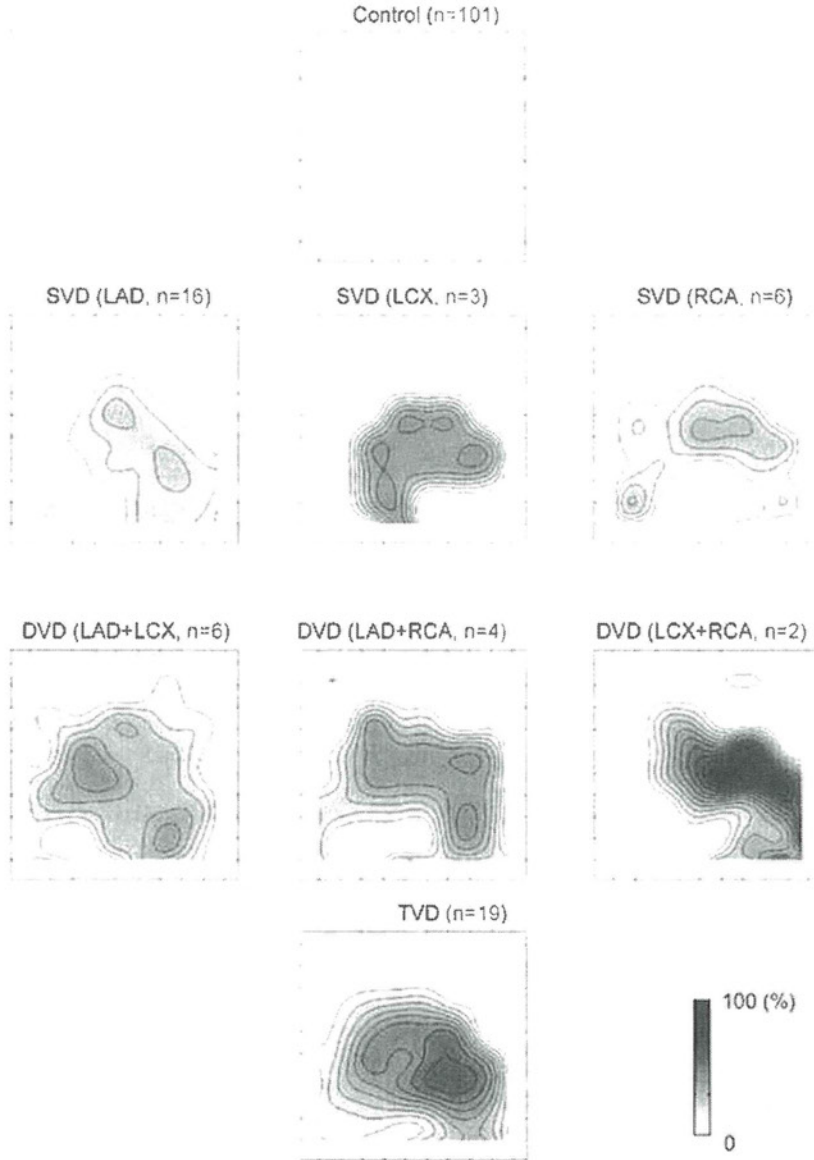


Figure 5. Two-dimensional frequency distribution of abnormal current appearance in each lesion patient and control.

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 signals²⁰ 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

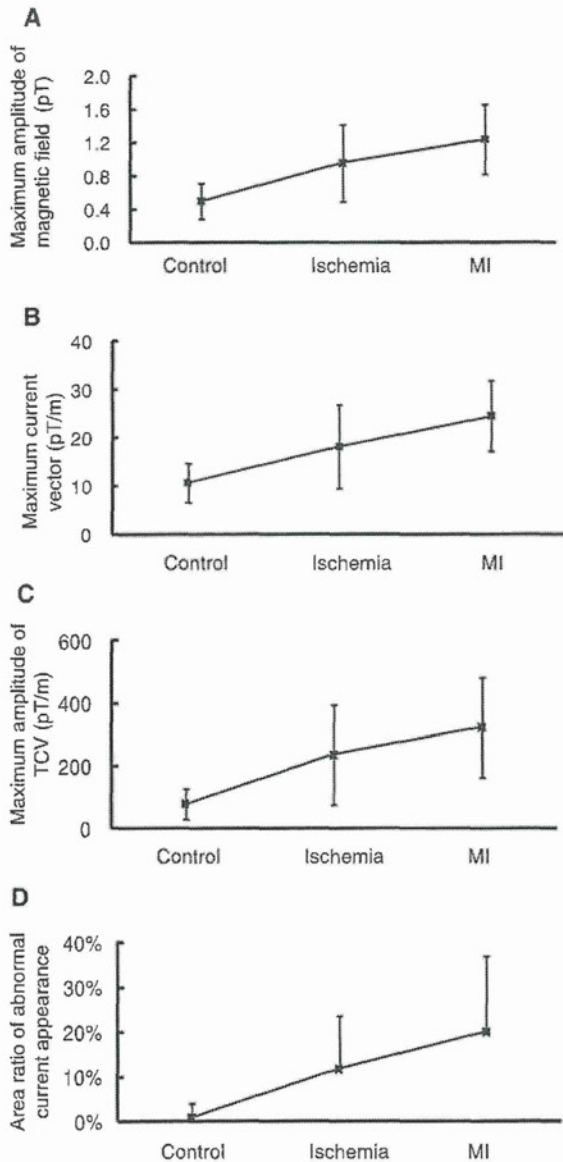


Figure 6. Relationships among control, ischemia, and myocardial infarction. (A) Maximum amplitude of magnetic field, (B) maximum current vector, (C) maximum amplitude of total current vector, (D) area ratio of abnormal current vector appearance.

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 muscle²² 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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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.

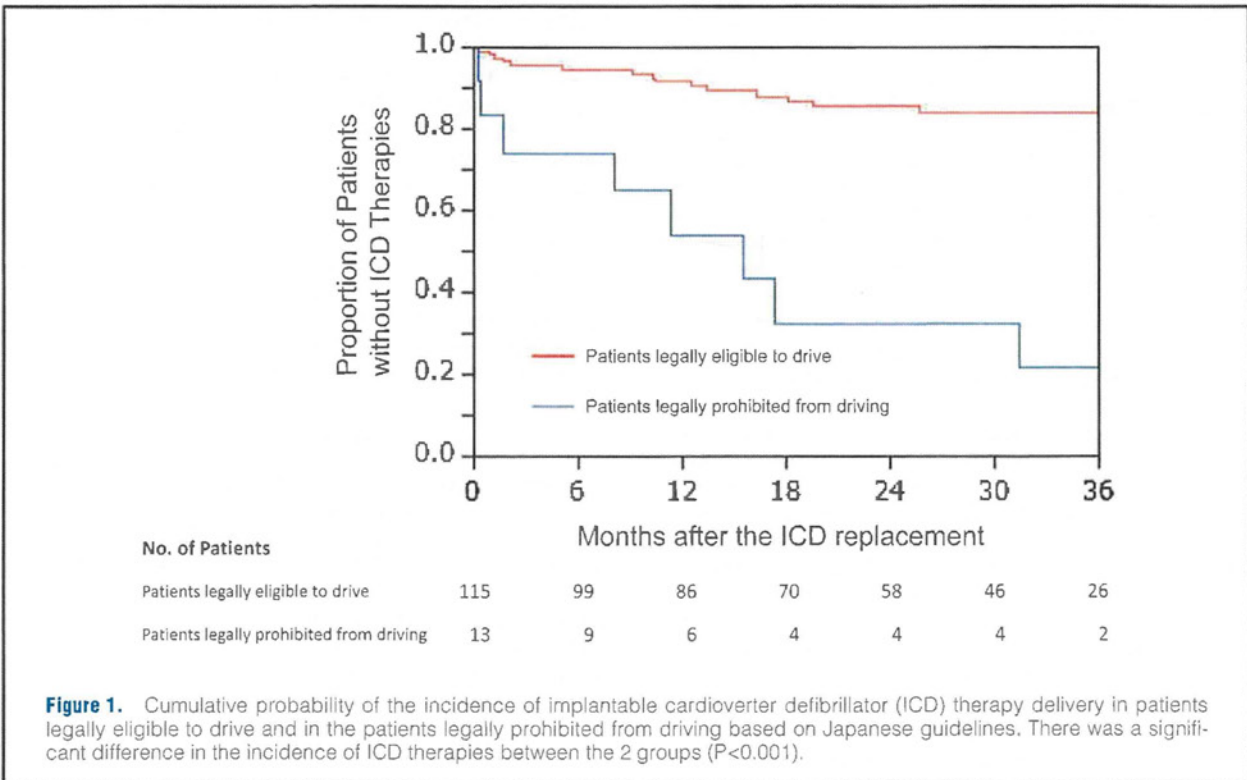


Table 5. Characteristics of the ICD Therapies in Patients Legally Eligible to Drive and in Patients Legally Prohibited From Driving

	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

Incident-free period before the ICD replacement	Proportion of patients who experienced ICD therapy after the ICD replacement		
	3 months	6 months	1 year
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%.

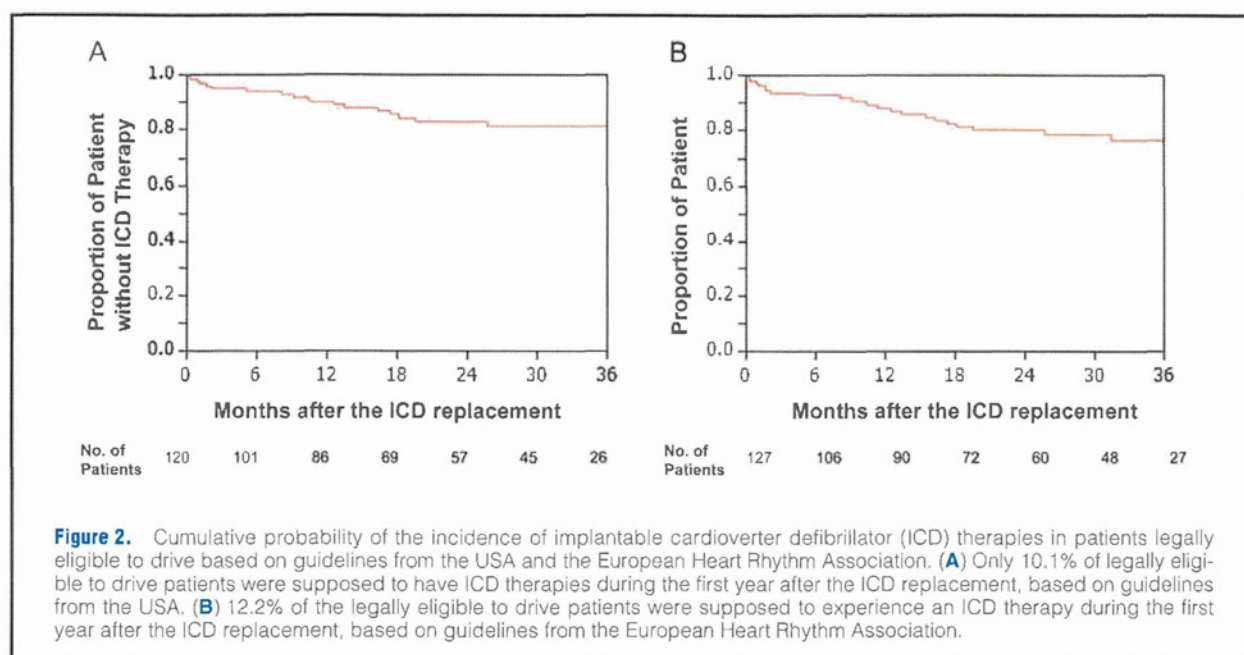
A Case of an Inappropriate Therapy Related to a Change in the Algorithm

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 Cardiology¹⁰ 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



the statement, they used the *Risk of Harm (RH) formula* ($RH=TD \times V \times SCI \times Ac$),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 transport¹¹ 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 pre-syncope, 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

integrity of the lead. The recovery and wound healing following this procedure takes a few days. A replacement of the ICD body only does not seem to affect the occurrence of either appropriate or inappropriate ICD therapies. However, any substantial evidence for this generally accepted notion remains scant. To the best of our knowledge, this is the first report to demonstrate that there was no difference in the incidence of ICD therapies before and after ICD replacements. Therefore, the replacement of the ICD body did not have an adverse effect on the ICD patients. In contrast, we found a case in which the replacement of the ICD affected the inappropriate ICD therapy. The cause of the inappropriate therapy was a change in the therapy algorithm. Essentially, an ICD using a similar algorithm as the previous one, and made by the same manufacturer, should be implanted in order to avoid any unnecessary inappropriate ICD therapies. Inappropriate therapies are often caused by supraventricular tachycardias including sinus tachycardia, and those arrhythmias occur more often during the patient's routine daily life than during their hospitalization. During hospitalization, patients often keep quiet and supraventricular tachycardias including sinus tachycardia are unlikely to happen. After the replacement of an ICD, it will take several days before the patient resumes their daily routine life. Therefore, we concluded that patients should refrain from driving for at least 1 week or so, including an extra few days before resuming their daily life.

In our study, the overall incidence of patients who experienced an ICD therapy was 12.2% and this number was lower than that in previous studies.^{20,21} This might be because our population included more Brugada syndrome patients and fewer patients with coronary artery disease. In fact, 22 asymptomatic Brugada patients were included in our study. This group of patients, although not statistically significant, showed better prognosis than the others (Log rank $P=0.18$). During the follow-up period of 2.15 ± 1.20 years, only 2 out of those 22 patients had ICD therapy. At this level of incidence, 12.2% is much lower than the threshold limit of 22%, which is defined in the consensus statement published by the ESC. Actually, in most patients, it is considered safe to give them permission to drive. However, our investigation showed that there was a high risk for those patients who have had recent ICD therapy. **Table 6** demonstrates that stricter regulations would result in the lower incidence of ICD therapy. However, even in patients with a 3 month incident-free period before the replacement, the annual incidence of ICD therapy after the replacement was 11.3%. This probability is still lower than acceptable level of 22%, as presented above.¹¹

As shown in **Figure 1**, the number of ICD therapies that occurred after device replacement in those patients legally prohibited from driving was high. Although the overall incidence of ICD therapy was reasonably low, the result might be due to the large number of low-risk patients such as asymptomatic Brugada patients. If we expand driving permission drastically, the incidence of cardiac events during driving could increase. Considering this fact, we need to carefully monitor high-risk patients with recent ICD therapies in order to prevent serious car accidents.

Defibrillation Threshold Test (DFT)

We performed a DFT in 115 out of 128 (89%) of patients. Some reports have been published with respect to the risk of DFT.^{22,23} Ventricular fibrillation and shocks during DFT could cause myocardial depression and might cause the subsequent VT/VF induction and result in frequent ICD discharge. However, the incidence of clinically significant myocardial depres-

sion and ventricular fibrillation after the DFT is limited and our data showed no significant effect on the rate of ICD therapies after the ICD replacement. We conclude that the DFT, at the time of ICD replacement, cannot affect the subsequent ICD discharge.

Study Limitations

This study had some limitations. First, one-third of our cohort consisted of Brugada syndrome patients, partly because the prevalence of Brugada syndrome is estimated to be high in Asian countries.²⁴ These patients often experience life-threatening arrhythmia or syncope during the resting state and sleep, and seldom develop life-threatening arrhythmias during driving. Second, this study was a retrospective cohort study. Third, a complete in-depth analysis of the distribution of the clinical variables in relation to the different manufacturers or different device models was not performed. And finally in this study, we did not separately analyze the patients who received appropriate and inappropriate therapies.²⁵

Conclusion

There was no evidence that ICD replacements increased the incidence of ICD therapies, if the replacements ICD were from the same manufacturer. Accordingly, these data do not support the unnecessary long restrictions on driving after an ICD replacement, and low risk patients should be allowed to resume driving as early as possible. In our opinion, we conclude that in patients who are allowed to drive before the ICD replacement within 1 week or so, including a few extra days to resume their usual life, this time frame should be adequate for the safety review. However, considering a case whereby ICD therapy was given after an ICD replacement, using one from another manufacturer, this conclusion should only apply to those patients receiving only the replacement of the generator and not a change in the programming of it.

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Disclosures

This manuscript represents original work that has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. All co-authors have read and approved the submission of the manuscript. There are no financial or other relations that could lead to a conflict of interest (Conflict of Interest: none declared).

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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 24h) occurred in 18/53 (34%) patients. According to multivariate Cox proportional hazard regression analysis, a duration of the terminal low amplitude signals of $<40\mu V$ (LAS40) (HR 1.4/10ms increase, 95% confidence interval (CI) 1.1–2.1; $P=0.0049$) or root mean square voltage of the last 40ms of the QRS complex (RMS40) (HR 0.88/ $1\mu V$, 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 $<0.5 \mu\text{V}$. The onset and offset of the QRS complex were determined by an algorithm that calculated the total QRS duration (TQRS), root mean square voltage of the last 40 ms of the QRS complex (RMS40) and the duration of the terminal low amplitude signals of $<40 \mu\text{V}$ 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.

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

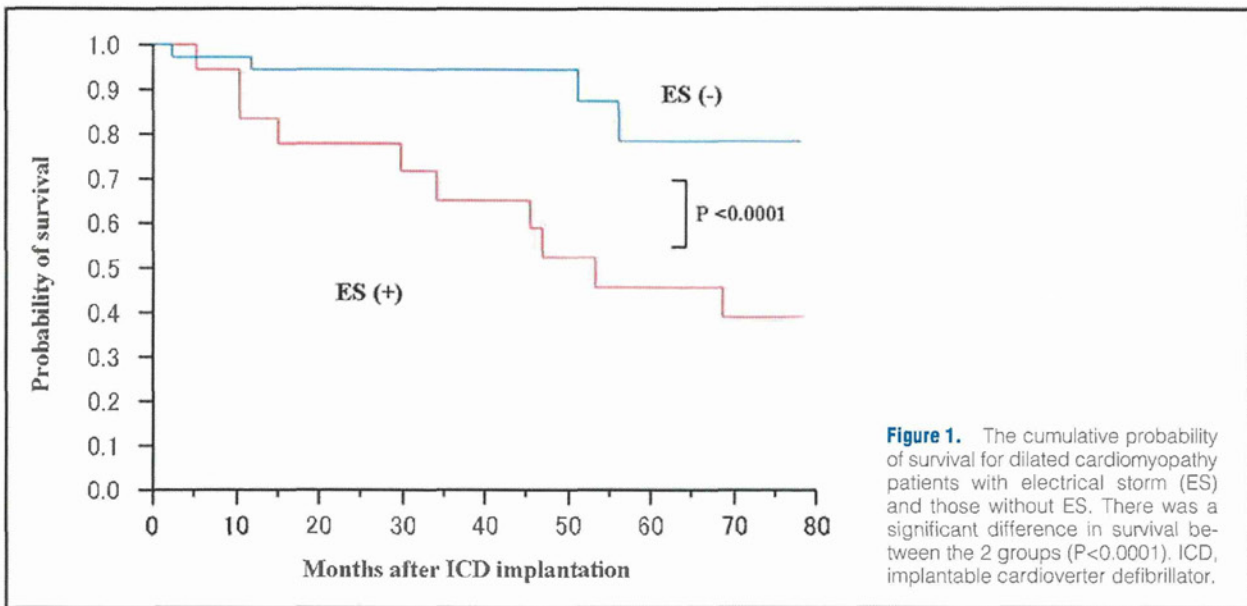
P-values of less than 0.05 were considered statistically significant. The results are expressed as frequencies and percentages for categorical variables and median or mean \pm SD

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

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

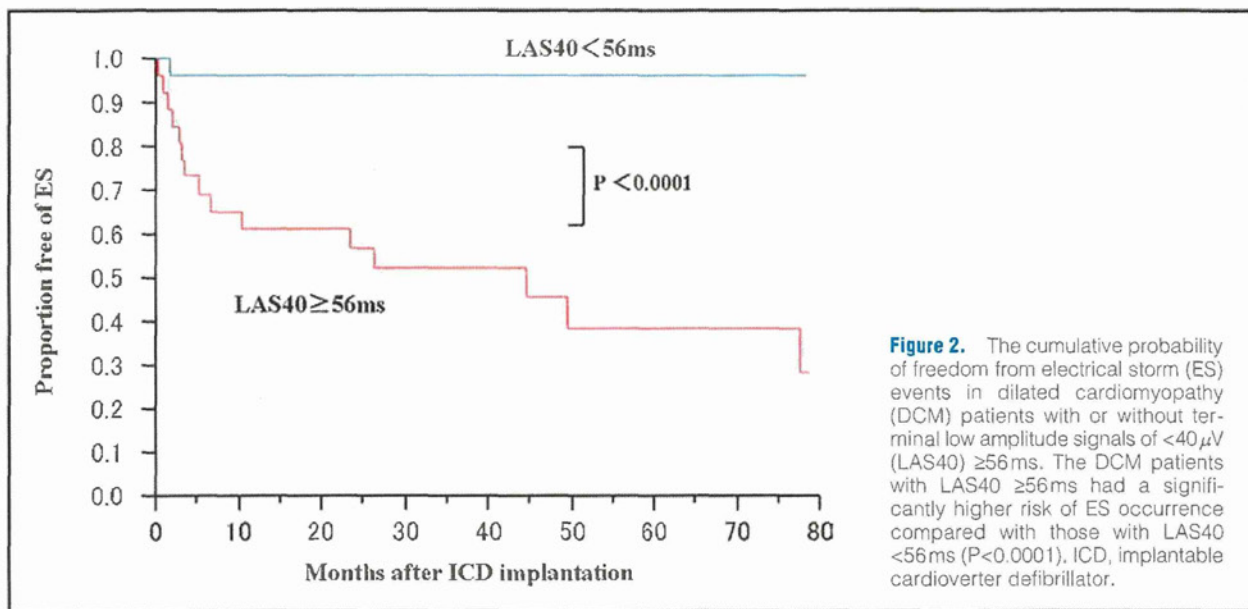
BMI, body mass index; NYHA, New York Heart Association; HF, heart failure; AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; TQRS, total filtered QRS duration; LAS40, the duration of the terminal low ($<40 \mu\text{V}$) 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.

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.

**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/m ²)	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 1.4/10 ms 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		
Spirolactone (%)	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.



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 $11.7\mu\text{V}$ to optimize the capability to predict ES. In cases with a cut-off value of LAS40 setting at 56 ms and RMS40 at $11.7\mu\text{V}$, 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 $11.7\mu\text{V}$ (0.87 vs 0.84, respectively). The Kaplan-Meier curves of the freedom from ES event between the group with or without LAS40 $\geq 56\text{ms}$ are illustrated in **Figure 2**. The DCM patients with LAS40 $\geq 56\text{ms}$ had a significantly higher risk of ES occurrence compared with those with LAS40 $< 56\text{ms}$ ($P < 0.0001$). The Kaplan-Meier curves of the freedom from ES event between

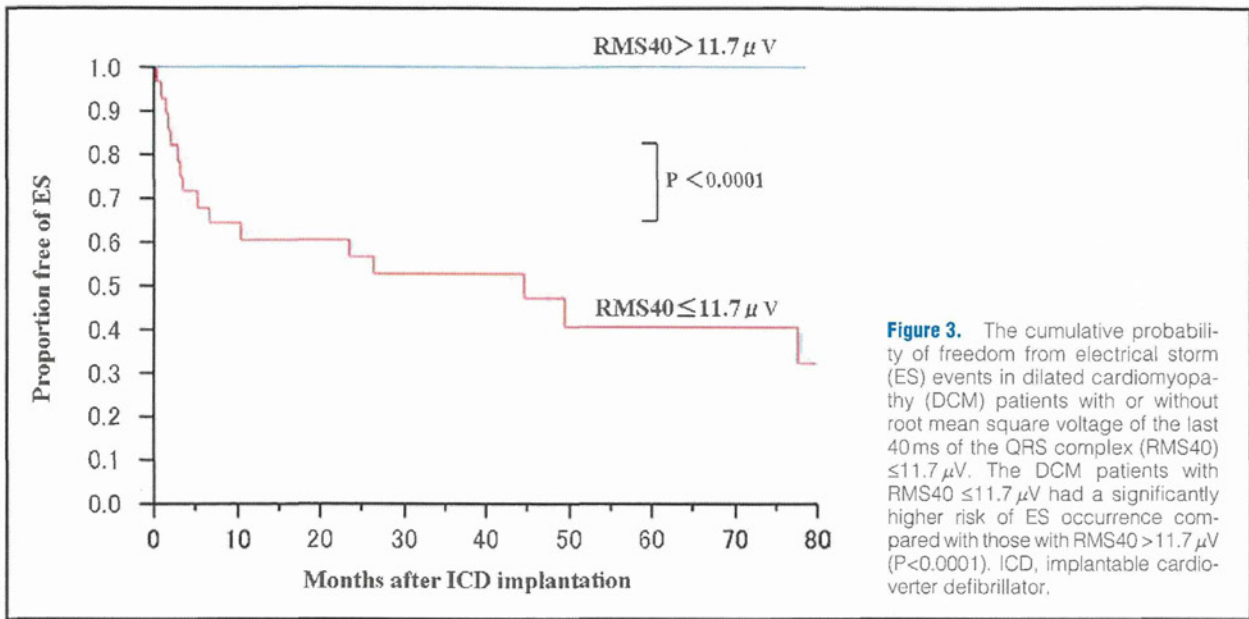


Figure 3. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without root mean square voltage of the last 40ms of the QRS complex (RMS40) $\leq 11.7 \mu\text{V}$. The DCM patients with RMS40 $\leq 11.7 \mu\text{V}$ had a significantly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

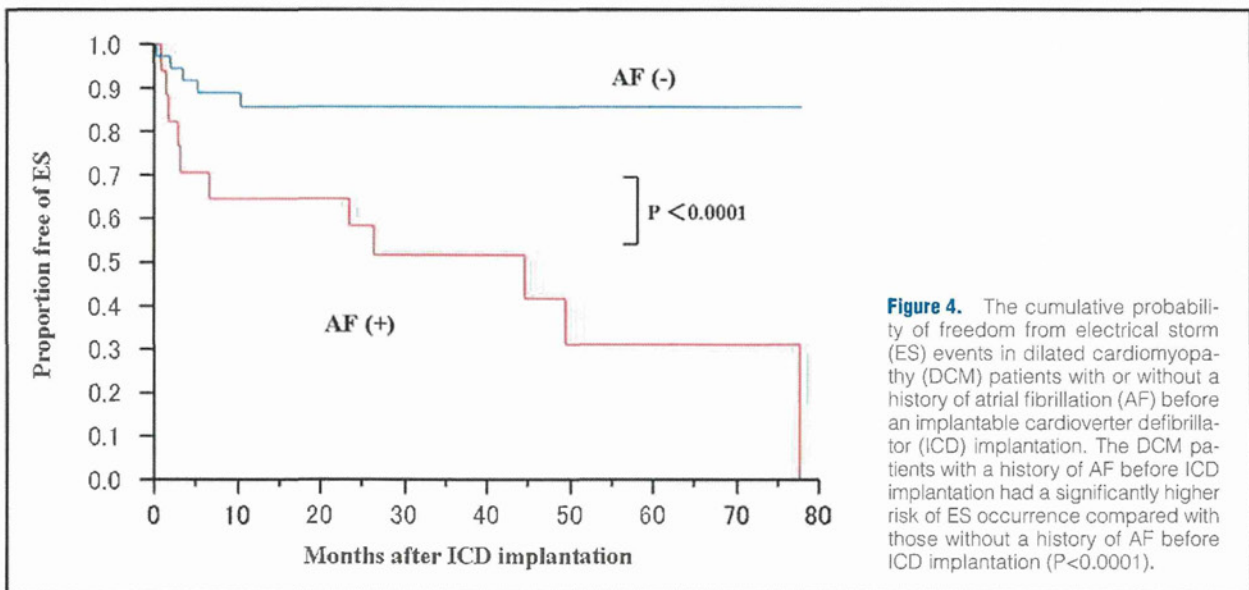


Figure 4. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without a history of atrial fibrillation (AF) before an implantable cardioverter defibrillator (ICD) implantation. The DCM patients with a history of AF before ICD implantation 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 $\leq 11.7 \mu\text{V}$ are shown in **Figure 3**. The DCM patients with RMS40 $\leq 11.7 \mu\text{V}$ had a significantly higher risk of ES occurrence compared with those with RMS40 $> 11.7 \mu\text{V}$ ($P < 0.0001$). 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 $\leq 11.7 \mu\text{V}$. As **Figure 5** shows, when using the combination of these independent predictors (AF and LAS40 ≥ 56 ms, or AF and RMS40 $\leq 11.7 \mu\text{V}$), 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

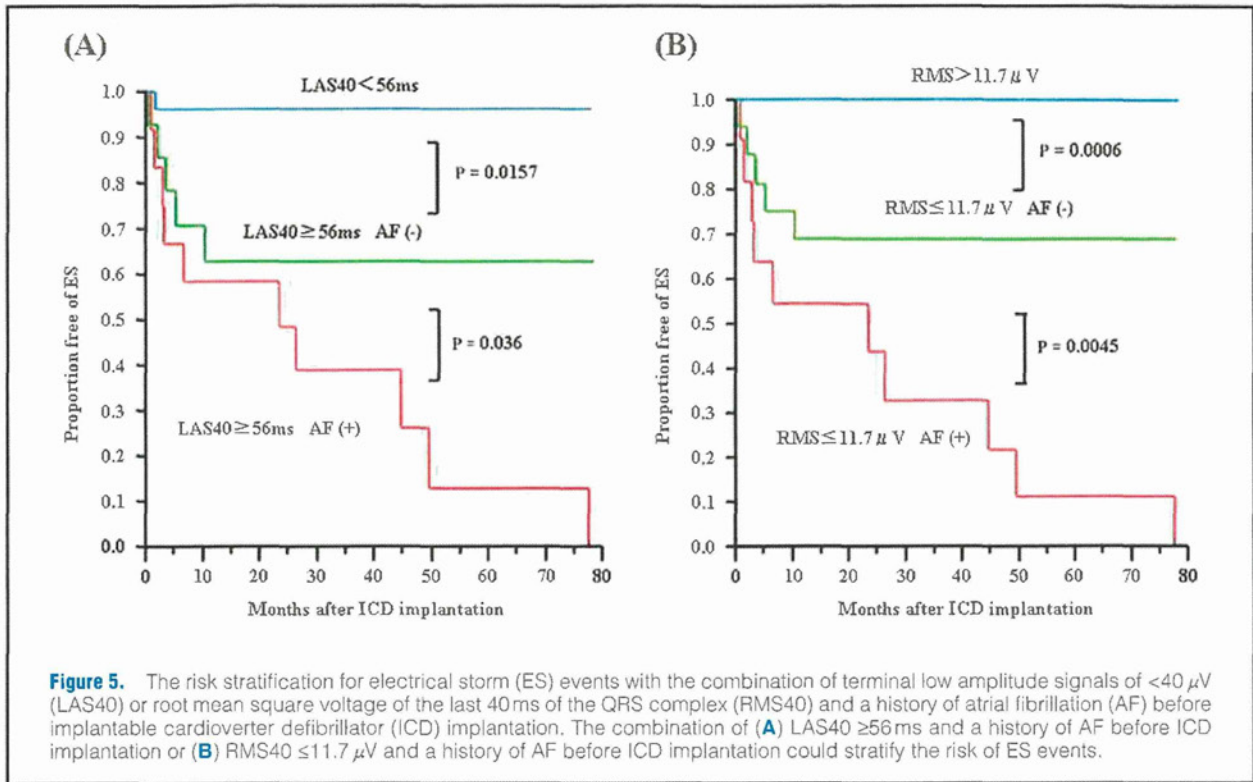


Figure 5. The risk stratification for electrical storm (ES) events with the combination of terminal low amplitude signals of <math><40 \mu\text{V}</math> (LAS40) or root mean square voltage of the last 40 ms of the QRS complex (RMS40) and a history of atrial fibrillation (AF) before implantable cardioverter defibrillator (ICD) implantation. The combination of **(A)** LAS40 ≥ 56 ms and a history of AF before ICD implantation or **(B)** RMS40 $\leq 11.7 \mu\text{V}$ 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 $1 \mu\text{V}$ increase in the value of RMS40 (HR 0.88/ $1 \mu\text{V}$, 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 $11.7 \mu\text{V}$, 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 $11.7 \mu\text{V}$ to stratify the risk of ES. However, the cut-off value of LAS40 was usually set at 38 ms and RMS40 at $20 \mu\text{V}$. 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 $20 \mu\text{V}$, 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 $<20 \mu\text{V}$ 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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Long QT syndrome with compound mutations is associated with a more severe phenotype: A Japanese multicenter study

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BACKGROUND: Long QT syndrome (LQTS) can be caused by mutations in the cardiac ion channels. Compound mutations occur at a frequency of 4% to 11% among genotyped LQTS cases.

OBJECTIVE: The purpose of this study was to determine the clinical characteristics and manner of onset of cardiac events in Japanese patients with LQTS and compound mutations.

METHODS: Six hundred three genotyped LQTS patients (310 probands and 293 family members) were divided into two groups: those with a single mutation ($n = 568$) and those with two mutations ($n = 35$). Clinical phenotypes were compared between the two groups.

RESULTS: Of 310 genotyped probands, 26 (8.4%) had two mutations in the same or different LQTS-related genes (compound mutations). Among the 603 LQTS patients, compound mutation carriers had significantly longer QTc interval (510 ± 56 ms vs

478 ± 53 ms, $P = .001$) and younger age at onset of cardiac events (10 ± 8 years vs 18 ± 16 years, $P = .043$) than did single mutation carriers. The incidence rate of cardiac events before age 40 years and use of beta-blocker therapy among compound mutation carriers also were different than in single mutation carriers. Subgroup analysis showed more cardiac events in LQTS type 1 (LQT1) and type 2 (LQT2) compound mutations compared to single LQT1 and LQT2 mutations.

CONCLUSION: Compound mutation carriers are associated with a more severe phenotype than single mutation carriers.

KEYWORDS Compound; Gene; Long QT syndrome; Mutation

ABBREVIATION QTS = long QT syndrome

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Introduction

Congenital long QT syndrome (LQTS) is a heterogeneous disease characterized by prolonged ventricular repolariza-

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tion and episodes of syncope and/or life-threatening cardiac arrhythmias, particularly polymorphic ventricular tachycardia.¹ Several disease-causing genes have been identified, including genes encoding cardiac ion channel-composing proteins, namely, *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), *KCNE2* (LQT6), *KCNJ2* (LQT7), and *CACNA1C* (LQT8), and genes encoding a family of versatile membrane adapters, namely, *ANK2* (LQT4), *CAV3* (LQT9), *SCN4B* (LQT10), *AKAPs* (LQT11), and *SNTA1* (LQT12).^{2–5} Two modes of inheritance are involved in this syndrome, which exhibits both an autosomal dominant and an autosomal recessive pattern. The majority of LQTS cases are inherited in an autosomal dominant fashion. This pattern, which has been named as Romano-Ward syndrome,^{6,7} can result from a single mutation in one