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Effect of sodium-channel blockade on early repolarization in inferior/lateral leads in patients with idiopathic ventricular fibrillation and Brugada syndrome

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BACKGROUND A high incidence of early repolarization (ER) pattern in the inferolateral leads has been reported in patients with idiopathic ventricular fibrillation (IVF). Brugada syndrome (BS) is characterized by J-point or ST-segment elevation in the right precordial leads and ventricular fibrillation, and some patients with BS also have ER in the inferolateral leads.

OBJECTIVE To compare the clinical characteristics and effects of sodium-channel blockade on ER between IVF patients with ER (early repolarization syndrome [ERS]) and BS patients with or without ER.

METHODS Fourteen patients with ERS and 21 patients with BS were included in this study. ER was defined as an elevation of at least 0.1 mV from baseline in the QRS–T junction in the inferorolateral leads. Provocative tests with sodium-channel blockers were conducted in all patients with ERS to distinguish ERS from BS.

RESULTS In the ERS group, all patients were male and most patients experienced ventricular fibrillation during sleep or low activity (79%). ER was attenuated by sodium-channel blockers in most patients with ERS (13/14, 93%) and BS (5/5, 100%), whereas ST-segment elevation was augmented in the right precordial leads in the BS group. The rates of positive late potentials were significantly higher in the BS group (60%) than in the ERS group (7%) ($P < .01$).

CONCLUSIONS Some similarities were observed between ERS and BS, including gender, arrhythmia triggers, and response of ER to sodium-channel blockers. Unlike the ST segment in the right precordial leads in BS, ER was attenuated in patients with both ERS and BS, suggesting a differential mechanism between ER in the inferolateral leads and ST elevation in the right precordial leads.

KEYWORDS Early repolarization; J wave; Idiopathic ventricular fibrillation; Brugada syndrome; Sudden death; Sodium-channel blocker

ABBREVIATIONS **BS** = Brugada syndrome; **ECG** = electrocardiogram; **ER** = early repolarization; **ERS** = early repolarization syndrome; **IVF** = idiopathic ventricular fibrillation; **LPs** = late potentials; **QTc** = corrected QT interval; **SAECG** = signal-averaged electrocardiogram; **SCD** = sudden cardiac death; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Early repolarization (ER) pattern is often found in the general population and has been considered a benign electrocardiographic finding. Its prevalence has been estimated to be between 1% and 5% of healthy adults.[1–4] Idiopathic ventricular fibrillation (IVF) presenting prominent ST-segment elevation in the inferior leads has been considered as a variant of Brugada syndrome (BS).[5,6] BS[7] is characterized by ST-segment elevation in the right precordial leads V1 to V3 and is considered to have a high propensity toward sudden cardiac death (SCD).[8,9] Recently, several reports have suggested the association of IVF with ER in the inferior and/or lateral lead in the electrocardiogram (ECG).[3,10–14] ER is reported to be found more frequently among patients with IVF than among healthy control subjects.[10,15] However, little is known about the clinical and electrocardiographic characteristics and the pharmacological response of ER in patients with IVF and BS associated with ER and their different re-

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sponse from that of ST elevation in the right precordial leads in patients with BS. The present study aimed to investigate the similarities and differences between IVF with ER (early repolarization syndrome [ERS]) and BS with or without ER.

Methods

Patient characteristics

Among 38 patients with IVF, admitted to the National Cerebral and Cardiovascular Center between 1994 and 2009, ER in the inferior and/or lateral ECG leads was recorded in 14 patients (37%). These 14 patients were included in this study as an ERS group (all males, aged 27–64 years, mean age 44.7 ± 13.6 years). Twenty-one patients with BS with a history of ventricular fibrillation (VF) or aborted SCD were also included in this study. According to the published guidelines,[16,17] patients were diagnosed as suffering from IVF if they had no structural heart disease confirmed by noninvasive studies (physical examination, ECG, exercise stress test, echocardiogram, and cardiac magnetic resonance imaging or computed tomography) and invasive studies (coronary angiography and left ventricular cineangiography). Long QT syndrome (corrected QT [QTc] interval ≥440 millisecond), short QT syndrome (QTc interval <340 millisecond), and BS were also excluded to diagnose a patient as suffering from IVF. To exclude BS, all subjects in the ERS group were proven to be negative with a pharmacological challenge with pilsicainide.[8,18]

The BS group consisted of 21 patients (19 males, aged 20–64 years, mean age 39.7 ± 12.6 years) with an episode of documented VF or aborted SCD. Eleven had a spontaneous type 1 ECG, and in the remaining, it was induced by a sodium-channel blocker. Ethical approval of the present study was obtained from the Institutional Review Committee of the National Cerebral and Cardiovascular Center.

Electrocardiography

All available conventional ECGs (25 mm/s, 10 mm/mV) were investigated in the search for ER. ER was defined as an elevation of at least 1 mm (0.1 mV) in the J point (QRS–ST junction) in at least 2 leads (Figure 1), either as QRS slurring (smooth transition from QRS to the ST segment) or as notching (a positive J deflection inscribed on the S wave).[10] The inferior (II, III, and aVF) and lateral (I, aVL, and V4–V6) leads were evaluated. To exclude BS, no J-point elevation must exist in the right precordial leads (V1–V3).

All ECGs were interpreted blindly by 2 independent cardiologists (H.K., W.S.). The following parameters were assessed in lead II, which include P-wave duration and PQ and RR intervals. QRS duration and QT interval were assessed in leads II and V5. The QTc interval was calculated using Bazett's method. The amplitude of ER was assessed in the inferior leads (II, III, and aVF), the lateral leads (I, aVL, and V4–V6), or both, and the maximum ER amplitude was measured. We selected leads II and V5 as representative of inferior and lateral leads for the analysis of ER amplitude.

BS was diagnosed when a type 1 coved-type ST-segment elevation (≥0.2 mV at J point) was observed in >1 of the right precordial leads (V1–V3) in the presence or absence of

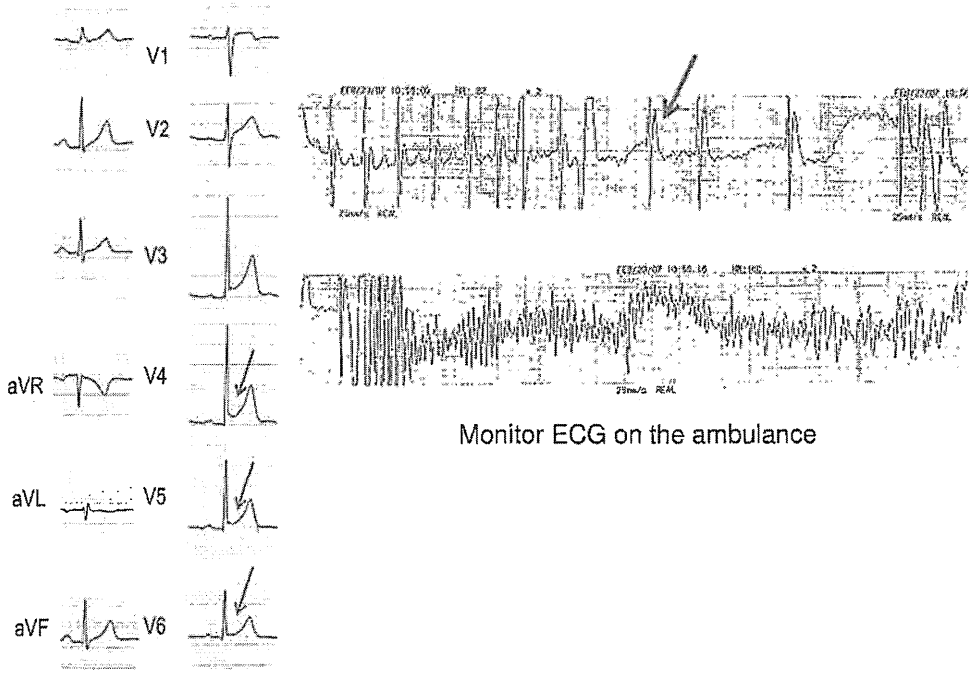

Figure 1 **A:** Twelve-lead ECG in a patient with early repolarization syndrome. ER (arrow) was seen in the lateral leads (V4–V6) under baseline conditions. **B:** Monitor ECG recorded during the arrhythmic periods in the same patient showed a consistent increase in the amplitude of ER, followed by initiation of ventricular fibrillation. ECG, electrocardiogram; ER, early repolarization.

a sodium-channel blocker in conjunction with documented VF or polymorphic ventricular tachycardia (VT).

Drug challenge test

The drug challenge test was performed with intravenous pilsicainide (1 mg/kg, maximum 50 mg, 5 mg/min) or flecainide (2 mg/kg, maximum 100 mg, 10 mg/min). The test result was considered positive if a type 1 Brugada ECG appeared in >1 right precordial lead (V1–V3). Once again, we excluded all patients with IVF but without sodium-channel blocker challenge test from our study to clarify the diagnosis of ERS.

Late potentials

Late potentials (LPs) were analyzed by using a signal-averaged electrocardiogram (SAECG) system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). Three parameters were assessed by using a computer algorithm: (1) total filtered QRS duration (f-QRS), (2) duration of low-amplitude signals <40 μV of the filtered QRS complex (LAS_{40}), and (3) root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complexes (RMS_{40}). LPs were considered positive when at least 2 of the 3 parameters were abnormal: f-QRS >120 millisecond, LAS_{40} >38 millisecond, and RMS_{40} <18 μV.

Statistical analysis

Continuous variables were expressed as mean value ± SD. A comparison between the 2 groups was performed with Student's t test for paired data. Categorical variables were compared with Fisher's exact test. A P value of <.05 was regarded as being significant.

Results

Clinical and electrocardiographic characteristics

In the BS group, 9 of the 21 patients (43%) with BS showed ER in the inferior and/or lateral leads. A comparison of the clinical and electrocardiographic characteristics of the 14 ERS group patients, 21 BS group patients, and 9 BS patients with ER is shown in Table 1. The average age of 9 BS patients with ER was lower than that of the ERS group. Except for that, no significant differences were observed in baseline clinical characteristics with respect to age, gender, family history of SCD, and activity at the time of cardiac arrest. The number of premature ventricular complexes during 24-hour Holter ECG was not different between the 2 groups.

Regarding SAECG parameters, the values of f-QRSd, LAS_{40}, and RMS_{40} in 14 ERS group patients were 97.8 ± 8.1 millisecond, 29.8 ± 5.2 μV, and 50.0 ± 24.2 millisecond, respectively. The corresponding values in 21 BS group patients were 119.8 ± 17.3 millisecond, 47.0 ± 19.2 μV, and 17.8 ± 13.4 millisecond, respectively. All these parameters were significantly different between the 2 groups. LPs were positive in 1 of the 14 patients (7%) in the ERS group and in 12 of the 20 patients (60%) in the BS group. The rate of positive LPs was significantly higher in the BS group than in the ERS group (P <.01). We also compared the SAECG parameters and the rate of positive LPs between 14 ERS group patients and 9 BS patients with ER. The tendency was similar to the comparison between 14 ERS group patients and 21 BS group patients; however, there were no significant differences in the LAS_{40} and rate of LPs because of the small number of BS patients with ER.

Table 1 Clinical and electrocardiographic characteristics in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Group			P value	
	ERS (n = 14)	BS (n = 21)	BS with ER (n = 9)	ERS vs BS	ERS vs BS with ER
Clinical characteristics					
Age (y), mean ± SD	44.7 ± 13.6	39.7 ± 12.6	33.3 ± 10.3	NS	.045
Male gender, n/N	14/14	19/21	7/9	NS	NS
Family history of sudden cardiac death, n/N (%)	0/14 (0%)	1/21 (5%)	1/9 (11%)	NS	NS
Activity at the time of cardiac arrest, n (%)					
Sleep	3 (21%)	9 (42%)	5 (55%)	NS	NS
Rest	8 (57%)	10 (48%)	3 (33%)	NS	NS
Others	3 (21%)	2 (10%)	1 (11%)	NS	NS
Electrocardiographic characteristics					
Presence of ER, n/N (%)	14/14 (100%)	9/21 (43%)	9/9 (100%)	<.01	NS
Holter ECG, PVC in 24 h, mean ± SD	49.4 ± 169.3	1.9 ± 4.2	2.3 ± 4.4	NS	NS
Signal-averaged electrocardiography, mean ± SD					
f-QRSd (ms)	97.8 ± 8.1	119.8 ± 17.3	111.6 ± 11.5	<.0001	<.01
LAS_{40} (μV)	29.8 ± 5.2	47.0 ± 19.2	33.8 ± 14.5	<.01	NS
RMS_{40} (ms)	50.0 ± 24.2	17.8 ± 13.4	23.4 ± 14.2	<.0001	<.01
Abnormal SAECG, n/N (%)	1/14 (7%)	12/20 (60%)	4/9 (44%)	<.01	NS

Percentages may not total 100 because of rounding.

BS, Brugada syndrome; ECG, electrocardiogram; ER, early repolarization; ERS, early repolarization syndrome; f-QRSd, filtered QRS duration; LAS_{40}, duration of low-amplitude signals <40 μV of QRS in the terminal filtered QRS complex; NS, not significant; PVC, premature ventricular contraction; RMS_{40}, root-mean-square voltage of the terminal 40 millisecond of the filtered QRS complex; SAECG, signal-averaged ECG.

Table 2 Baseline electrocardiographic parameters and their changes after administration of a sodium-channel blocker in the early repolarization syndrome group, the Brugada syndrome group, and the Brugada syndrome with ER group

	Mean ± SD			*P* value	
	ERS (n = 14)	BS (n = 12)	BS with ER (n = 5)	ERS vs BS	ERS vs BS with ER
RR II (ms)	951 ± 116	930 ± 116	1024 ± 46	NS	NS
ΔRR II (ms)	−71 ± 41	−12 ± 17	−32 ± 62	<.05	NS
P II (ms)	104 ± 19	110 ± 16	112 ± 13	NS	NS
ΔP II (ms)	10 ± 9	21 ± 13	24 ± 16	<.05	<.05
PQ II (ms)	179 ± 34	191 ± 33	178 ± 28	NS	NS
ΔPQ II (ms)	30 ± 9	28 ± 14	38 ± 8	NS	NS
QRS II (ms)	90 ± 13	97 ± 18	90 ± 20	NS	NS
ΔQRS II (ms)	10 ± 10	23 ± 21	14 ± 21	NS	NS
QRS V5 (ms)	84 ± 8	91 ± 19	82 ± 21	NS	NS
ΔQRS V5 (ms)	13 ± 8	29 ± 18	28 ± 8	<.05	<.01
QT II (ms)	377 ± 19	370 ± 14	374 ± 15	NS	NS
ΔQT II (ms)	10 ± 14	28 ± 18	16 ± 5	NS	NS
QTcII (ms)	388 ± 20	385 ± 24	370 ± 13	NS	NS
ΔQTcII (ms)	10 ± 14	29 ± 18	16 ± 5	<.05	NS
QT V5 (ms)	376 ± 26	372 ± 17	376 ± 15	NS	NS
ΔQT V5 (ms)	6 ± 18	38 ± 23	14 ± 11	<.01	NS
QTcV5 (ms)	387 ± 23	387 ± 24	372 ± 12	NS	NS
ΔQTcV5 (ms)	7 ± 19	40 ± 25	14 ± 11	<.01	NS

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; P = P-wave duration; PQ = PQ interval; QRS = QRS duration; QT = QT interval; QTc = corrected QT interval; RR = RR interval.

Sodium-channel blocker infusion test

The sodium-channel blocker infusion test was performed in 12 of the 21 patients with BS, and the test result was positive in all 12 patients. We compared the pharmacological responses of several ECG parameters to a sodium-channel blocker between 14 patients with ERS and 12 patients with BS (Table 2). There were no significant differences in the baseline ECG parameters, including RR interval, P-wave duration, PQ interval, QRS duration, and QT interval in any leads. Shortening of RR (ΔRR II) was significantly larger in the ERS group. Prolongation of P-wave duration (ΔP II), QRS duration (ΔQRS V5), and QTc interval (ΔQTc II, ΔQTc V5) was significantly larger in the BS group compared with that in the ERS group.

Among 9 BS patients with ER, the sodium-channel blocker test was performed in 5 patients. We also compared the ECG parameters between 14 ERS group patients and 5 BS patients with ER (Table 2). Prolongation of P-wave duration (ΔP II) and QRS duration (ΔQRS V5) was significantly larger in the BS with ER group compared with that in the ERS group.

The ER amplitude and its responses to sodium-channel blockers between 14 ERS group patients and 5 BS patients with ER are shown in Table 3. In the ERS group, ER was observed in the inferior leads (II, III, and aVF) in 9 patients, in the lateral leads (I, aVL, and V4–V6) in 8 patients, and in both the inferior and lateral leads in 3 patients. In the 9 BS patients with ER, ER was observed in the inferior leads in 6 patients, in the lateral leads in 8 patients, and in both the inferior and lateral leads in 5 patients. The baseline maximum ER amplitude among the inferolateral leads (pre-ER max) in the BS group tended to be higher than in the ERS group (0.244 ± 0.082 vs 0.162 ± 0.069 mV; $P = .057$). The baseline ER amplitude in the inferior lead (pre-ER II) was significantly higher in the BS group than in the ERS group (0.236 ± 0.081 vs 0.120 ± 0.033 mV; $P < .05$). After administration of a sodium-channel blocker, the ER ampli-

Table 3 Amplitude of ER in leads II and V5 before and after the administration of a sodium-channel blocker test in the early repolarization syndrome group and the Brugada syndrome with ER group

Maximum amplitude of ER in any inferolateral leads (mV)	Mean ± SD		
	ERS (n = 14)	BS with ER (n = 5)	*P* value
Pre-ER max	0.162 ± 0.069	0.244 ± 0.082	NS
Post-ER max	0.081 ± 0.061*	0.124 ± 0.096*	NS
ΔER	0.080 ± 0.067	0.120 ± 0.058	NS
Amplitude of ER in the inferior lead (II) (mV)	**ERS (n = 9)**	**BS (n = 5)**	
Pre-ER II	0.120 ± 0.033	0.236 ± 0.081	<.05
Post-ER II	0.091 ± 0.054*	0.104 ± 0.086*	NS
ΔER II	0.028 ± 0.051	0.132 ± 0.068	<.05
Amplitude of ER in the lateral lead (V5) (mV)	**ERS (n = 8)**	**BS (n = 5)**	
Pre-ER V5	0.116 ± 0.032	0.215 ± 0.092	NS
Post-ER V5	0.010 ± 0.022*	0.137 ± 0.094*	NS
ΔER V5	0.106 ± 0.026	0.077 ± 0.071	NS

BS = Brugada syndrome; ER = early repolarization; ERS = early repolarization syndrome; max = maximum; pre = before sodium-channel blocker test; post = after sodium-channel blocker infusion; Δ = change.
*P <.05 vs pre.

tude was attenuated in all 5 patients with BS (100%) and in 13 of 14 patients with ERS (93%). ER attenuation was occasionally associated with the appearance of an S wave in both the groups (Figure 2). Therefore, the maximum ER amplitude (ER max), ER amplitude in the inferior lead (ER II), and ER amplitude in the lateral lead (ER V5) all were significantly decreased after the administration of sodium-channel blockers ($P < .05$). Figure 3 illustrates the differential response to sodium-channel blockers between the ER in the inferolateral leads and the J point and ST segment in the right precordial leads in a patient with BS. The coved-type (type 1) ECG was unmasked and the J point in the right precordial leads (V1–V3) was augmented by the sodium-channel blocker, whereas the ER amplitude in the inferolateral leads (II, III, aVF, and V4–V6) was attenuated (Figure 3B).

Discussion

The ER pattern in the inferior and/or lateral leads had been considered benign, and it is often found in healthy young individuals. Recently, several reports have attracted increasing attention to the association of IVF with ER in the inferior and/or lateral leads.[5,10,19–21] Haissaguerre et al[10] reported that ER was more frequently recognized in patients with IVF than in control subjects and that there was a higher incidence of recurrent VF in case subjects with ER than in those without. Rosso et al[15] also reported that ER was found more frequently among patients with IVF than among healthy control subjects. On the other hand, BS is also characterized by a high incidence of VF without structural heart disease. The Brugada Consensus Report proposed that type 1 coved-type ST-segment elevation in the right precordial lead (V1–V3) in the absence or presence of a sodium-channel blocker was required to diagnose BS.[22] Considering this diagnostic criterion, the sodium-channel blocker challenging test is essential to exclude BS. In order to investigate pure ERS, the sodium-channel blocker challenging test should be performed before the diagnosis of ERS. Unlike previous studies,[10,15] we conducted the sodium-channel blocker challenging test in all 14 patients with ERS to exclude BS in the present study.

Intravenous administration of sodium-channel blockers has been used to unmask the Brugada ECG pattern in patients with BS.[23] On the other hand, in most patients associated with ER in both the ERS group and the BS group of the present study, the administration of a sodium-channel blocker induced the attenuation or disappearance of the ER and appearance of an S wave. Attenuation of the ER in the inferolateral leads appears to be due largely to a slowing of the transmural conduction so that inscription of the ER occurs later on the descending limb of the QRS in both the ERS group and the BS group. The S-wave appearance in the inferolateral leads is also probably due to the conduction delay induced by sodium-channel blockers. This may indicate the differential mechanism between Brugada-type ST elevation in the right precordial lead of BS and ER in the inferolateral leads in both groups.

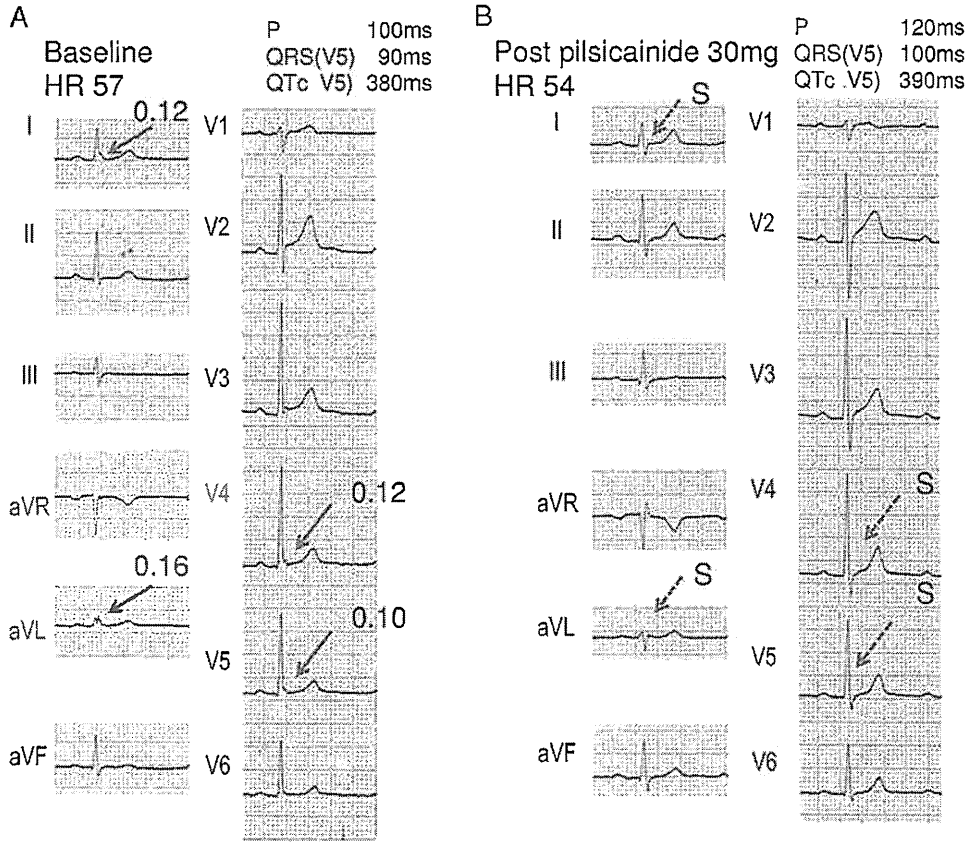

Figure 2 Twelve-lead ECGs in a patient with early repolarization syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the lateral leads (I, aVL, and V4–V5) under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide induced attenuation of ER and appearance of an S wave in the lateral leads (dashed arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization; S, S wave.

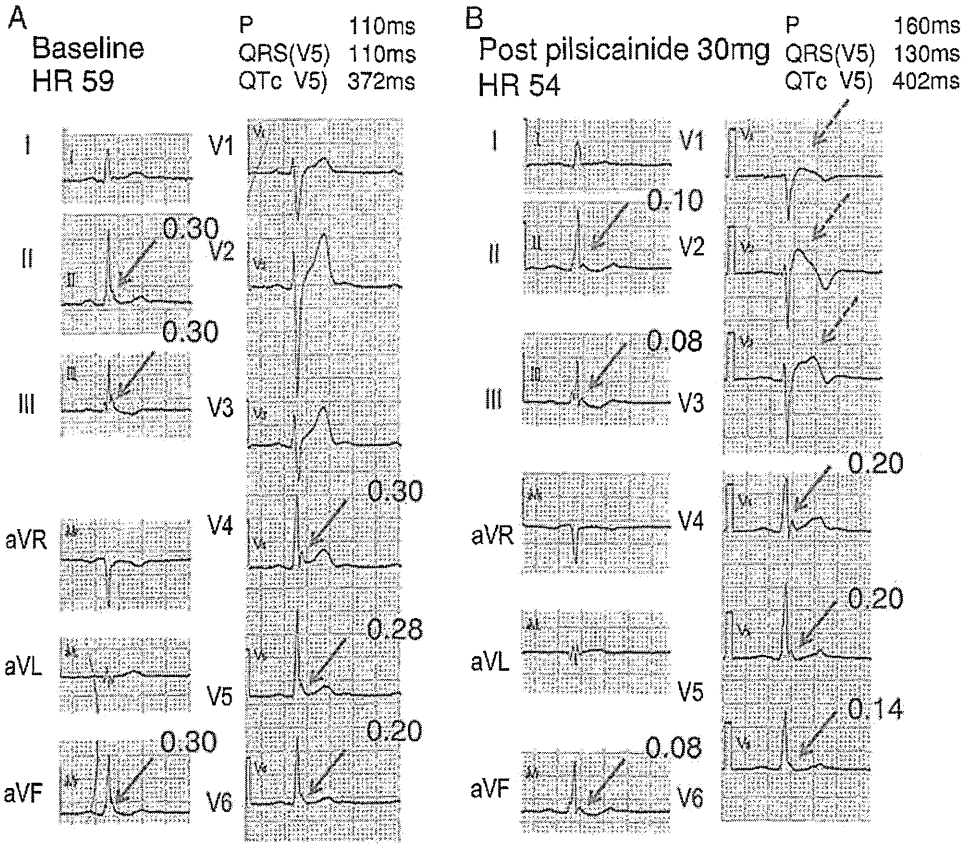

Figure 3 Twelve-lead ECGs in a patient with Brugada syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the inferior (II, III, and aVF) and lateral (V4–V6) leads under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide unmasked coved-type Brugada ECG and remarkably augmented the J point and ST segment in the right precordial leads (V1–V3) (**B**, dashed arrows), while ER was attenuated in the inferior and lateral leads (**B**, arrows). Numbers above the arrows indicate the amplitude of ER. ECG, electrocardiogram; ER, early repolarization.

Antzelevitch and Gan-Xin[24] have proposed a new concept that an outward shift in repolarizing current due to a decrease in sodium- or calcium-channel currents or an increase in outward currents such as a transient outward potassium current (I_{to}) can give rise to J-wave syndromes, which includes BS, ERS, hypothermia, and acute ischemia–induced VF. A prominent and pathological J wave, a slow upright deflection between the end of the QRS complex and the early portion of the ST segment, has been reported to be seen often in hypothermia.[25] However, the terms J-wave syndromes and ERS have not been properly defined.[26]

In some patients with BS of this study, type 1 Brugada ECG was unmasked by a sodium- channel blocker in the right precordial lead, while ER was attenuated in the inferolateral leads (Figure 3). Once again, this finding suggested the differential mechanism between Brugada-type ECG in the right precordial lead and ER in the inferolateral leads.

Moreover, as with a previous report,[27] the BS group showed significantly larger prolongation of P-wave duration, QRS duration, and QTc interval compared with the ERS group after a sodium-channel blocker infusion. Basic electrophysiology including animal or mathematical models must play an important role in determining whether the cellular mechanism of ST-segment elevation in the right precordial leads in BS and that of ER in the inferolateral leads in both ERS and BS differ or not.

Our study showed clinical characteristics of ERS to be similar to those of BS, including adult onset, male preponderance, cardiac events occurred at rest or during sleep, and rare ventricular arrhythmias on Holter ECG.[28,29] On the other hand, some apparent differences were found between the 2 groups, including LPs on the SAECG. All 3 parameters of the SAECG were significantly different between the 2 groups, and the positive rate of LPs was significantly lower in the ERS group than in the BS group. The rate of LPs has been previously reported to be high in BS.[30] On the other hand, Haissaguerre et al[10] also reported a relatively low rate (11%) of LPs in patients with ERS. LPs are reported to be not only highly prevalent in BS but also independent predictors of VT/VF inducibility.[27,31–33] LPs are also considered to be linked to VF inducibility during electrophysiological study and ventricular conduction delay during VF induction in patients with BS[28,34] as well as in patients with VT/VF associated with organic heart diseases. The ST-segment elevation in the right precordial leads and arrhythmogenicity in BS can be explained by both repolarization and depolarization abnormalities in right ventricular outflow.[9,35] The presence of LPs can be caused by conduction delay (depolarization abnormality) in the ventricle including the right ventricular outflow tract. On the other hand, from the experimental studies, LPs are explained on the basis of repolarization abnormality (late phase 2 upstroke and concealed phase 2 reentry) in the right ventricular outflow tract.[36] In the present study, the lower prevalence of LPs in the ERS group may indicate a differential substrate for VF in patients with ERS compared with that in patients with BS.

Conclusions

ER can be seen in some patients with IVF and in a subgroup of subjects with BS. Clinical similarities among them exist, including age, gender, and arrhythmia triggers. Response to sodium-channel blockade on ER in the inferolateral leads is the same in both groups: a consistent diminution in ER amplitude. This effect contrasts with the ST-segment elevation that is always observed in the right precordial leads in BS, thus arguing for different pathophysiological mechanisms.

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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.

Editorial p2283

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.

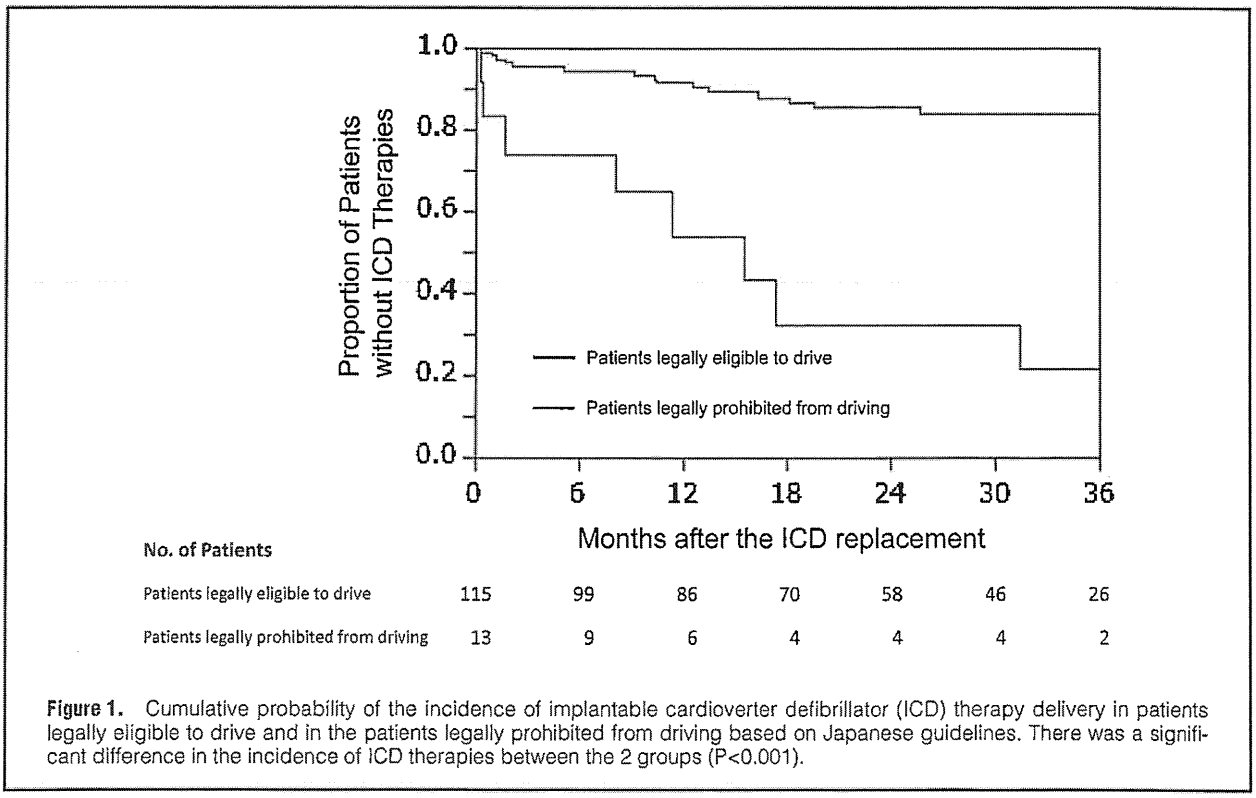

Figure 1. Cumulative probability of the incidence of implantable cardioverter defibrillator (ICD) therapy delivery in patients legally eligible to drive and in the patients legally prohibited from driving based on Japanese guidelines. There was a significant difference in the incidence of ICD therapies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

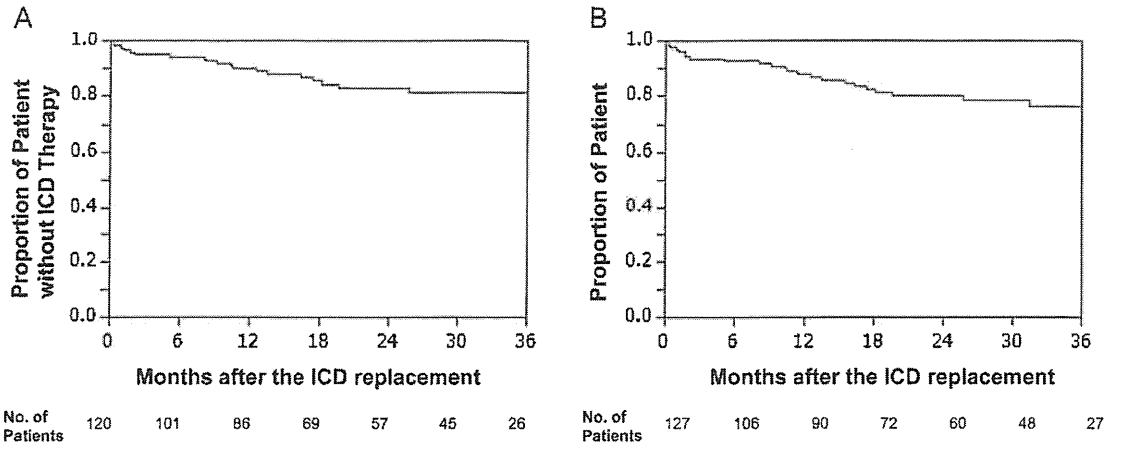

Figure 2. Cumulative probability of the incidence of implantable cardioverter defibrillator (ICD) therapies in patients legally eligible to drive based on guidelines from the USA and the European Heart Rhythm Association. (A) Only 10.1% of legally eligible to drive patients were supposed to have ICD 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

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 depression 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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Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life

A Nationwide Questionnaire Survey in Japan

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Background—Data on the clinical presentation and genotype-phenotype correlation of patients with congenital long-QT syndrome (LQTS) diagnosed at perinatal through infantile period are limited. A nationwide survey was conducted to characterize how LQTS detected during those periods is different from that in childhood or adolescence.

Methods and Results—Using questionnaires, 58 cases were registered from 33 institutions. Diagnosis (or suspicion) of LQTS was made during fetal life (n=18), the neonatal period (n=31, 18 of them at 0 to 2 days of life), and beyond the neonatal period (n=9). Clinical presentation of LQTS included sinus bradycardia (n=37), ventricular tachycardia/torsades de pointes (n=27), atrioventricular block (n=23), family history of LQTS (n=21), sudden cardiac death/aborted cardiac arrest (n=14), convulsion (n=5), syncope (n=5), and others. Genetic testing was available in 41 (71%) cases, and the genotype was confirmed in 29 (71%) cases, consisting of LQT1 (n=11), LQT2 (n=11), LQT3 (n=6), and LQT8 (n=1). Ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively observed in patients with LQT2, LQT3, and LQT8, as well as in those with no known mutation. In LQT1 patients, clues to diagnosis were mostly sinus bradycardia or family history of LQTS. Sudden cardiac death/aborted cardiac arrest (n=14) was noted in 4 cases with no known mutations as well as in 4 genotyped cases, although the remaining 6 did not undergo genotyping. Their subsequent clinical course after aborted cardiac arrest was favorable with administration of β-blockers and mexiletine and with pacemaker implantation/implantable cardioverter-defibrillator.

Conclusions—Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias, with only 7 deaths recorded. (***Circ Arrhythm Electrophysiol.* 2010;3:10-17.)**

Key Words: arrhythmia ■ long-QT syndrome ■ genes ■ death (sudden)

Congenital long-QT syndrome (LQTS) is an inherited disorder characterized by polymorphic ventricular tachycardia (VT), or torsades de pointes (TdP), syncope, and sudden cardiac death.[1] LQTS is often diagnosed in children from school age to young adulthood[2] and sometimes during fetal, neonatal, and infantile life.[3–5] Previous case reports

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Table 1. Questionnaire Items

1. Patient: Serial No. in each institution, initials, birth year, and month, sex
2. Age at diagnosis or suspicion (including gestational age for a fetus)
3. Clinical symptoms: Fetal arrhythmias, fetal heart failure, syncope, convulsion, heart failure, aborted cardiac arrest, others
4. ECG findings and arrhythmias (heart rate, QTc on ECG at presentation, sinus bradycardia, VT/TdP, atrioventricular block, other arrhythmias)
5. Family history of LQTS or other arrhythmias or sudden cardiac death (which member, and their outcome?)
6. Genotype
7. Treatment (acute therapy and maintenance therapy)
   pharmacotherapy (which drug, dose, age at initiation, and duration)
   device therapy (pacemaker implantation/implantable cardioverter-defibrillator) and age at application
8. Duration of follow-up
9. Outcome (alive or death, and neurological sequels of cardiac arrest)

suggest that the latter cases are at higher risk of development of life-threatening arrhythmias necessitating emergency treatment[3–5] and show higher mortality rates than the former age groups.[3,5–11] For example, recent progress in molecular biology has clarified that LQTS partly contributes to sudden infant death syndrome (SIDS).[12,13] Unfortunately, prenatal diagnosis of LQTS has been extremely difficult to confirm except for a limited number of cases for which prenatal gene screening[14] or fetal magnetocardiography (fMCG)[15–17] was applied.

Clinical Perspective on p 17

Thus, the clinical presentation, the genotype-phenotype correlation, and the outcome of patients with fetal, neonatal, or infantile presentation of LQTS remain to be elucidated. The purposes of this study were first, to report the findings of a nationwide survey conducted to define the clinical characteristics and the genotype-phenotype correlation, and second, to report the outcome of patients with LQTS diagnosed before birth and in the first year of life.

Methods

Population

The study population included fetuses, neonates, and infants (<1 year of age) diagnosed with LQTS based on ECG findings including prolonged QTc >0.46 seconds (using Bazett formula), with or without VT/TdP, who had no structural heart disease, family history of LQTS, or had undergone genetic testing. Those with normal QTc duration and no gene mutation known to cause LQTS were excluded. Patient data were collected using questionnaires. The form was sent to those councilors of the Japanese Society of Pediatric Cardiology and Cardiac Surgery who responded to a preliminary survey that they had 1 or more cases of LQTS diagnosed during fetal, neonatal, and infantile life. The items obtained from the responders are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba, and informed consent was obtained from each patient (or parents, if the patient was younger than 15 years of age) by a coordinator in charge in each institution before the patient's data were registered.

Genetic Analysis and Genotype-Phenotype Correlation

Genetic analyses were performed in 4 established laboratories in Japan. DNA was isolated from blood samples in each patient. Screening for mutations of at least 3 major genes causing LQTS (*KCNQ1, KCNH2, SCN5A*) was performed using polymerase chain reaction (PCR)/single-strand conformation polymorphism or denatured high-performance liquid chromatography analysis. For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI 3700 and ABI 3130xl, Applied Biosystems, Foster City, Calif). For those subjects in whom genotype was confirmed and those who underwent genetic analysis but found to have no mutation, genotype-phenotype correlations (or mutation-negative phenotype correlations) with the aforementioned items (Table 1) were investigated.

Statistical Analysis

All statistical calculations were conducted using the R software. Quantitative variables (heart rate [HR] and QTc) are presented as mean±SD and categorized variables (presence of FH, sinus bradycardia, VT/TdP, and atrioventricular block [AVB]) as proportions (percentages). One-way ANOVA was applied for comparisons of continuous variables, followed by pairwise comparisons with Bonferroni adjustment of probability values among 4 groups (LQT1, LQT2, LQT3, and mutation-negative groups). The equality of proportions for categorical variables among the 4 groups was examined by the χ^2 test (global test). When there was a significant difference in proportions, we performed pairwise comparisons between pairs of proportions with correction for multiple testing using Bonferroni inequality of probability values. Tests were 2-sided, and a probability value <0.05 was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Population

A total of 58 cases (all Japanese; males 30, females 28) were registered from 33 institutions. Forty-one were born during the last 10 years (between 1999 and 2008), 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. LQTS was diagnosed or suspected during fetal life at 18 to 40 weeks of gestation in 18 individuals, during neonatal life at 0 to 28 days in 31, and in infancy (<1 year) at 1 to 9 months in 9.

Clinical Features

For 18 fetuses with LQTS, clinical presentation (or clues to diagnosis or suspicion of LQTS) included bradycardia (15 cases), AVB (8 cases), VT/TdP (7 cases), and family history of LQTS (6 cases), including 1 family with a previous intrauterine death (items overlapped in some cases). Two fetuses were confirmed to be LQTS by fMCG, with QTc values of 570 and 680 on fMCG, and 590 and 700 on ECG soon after birth, respectively (these 2 cases have been reported previously).[16,17] No fetal death was noted in this group.

For 31 neonates with LQTS, the most frequent feature was sinus bradycardia (17 cases), followed by VT/TdP (15 cases), positive family history of LQTS (15 cases), including 1 with previous intrauterine death and 1 with infantile death, AVB (10 cases), syncope (5 cases), convulsion (5 cases), and others (items overlapped in some cases). Among the 31 neonatal cases, 18 (70%) were diagnosed within 2 days of life, and 8 of them had some significant fetal presentation (4 bradycardia or bradyarrhythmias, 4 tachyarrhythmias, and 1 hydrops), retrospectively.

As described above, the number of patients with LQTS diagnosed during infancy beyond the neonatal period was only 9. The clinical presentation of these patients included sinus bradycardia (5 cases), sudden cardiac death (SCD)/

aborted cardiac arrest (ACA) (5 cases), AVB (5 cases), VT/TdP (5 cases), and other miscellaneous abnormalities.

The ECG on diagnosis, or immediately after birth for fetal cases, showed that the HR and QTc interval (corrected using Bazett formula) ranged from 50 to 160 (102±28) bpm, and from 360 to 774 (563±70) ms, respectively.

Genotype-Phenotype Correlation

Among 41 patients who underwent genetic testing, mutations were identified in 29 (71%) cases; including *KCNQ1* gene mutations (LQT1) in 11, *KCNH2* mutations (LQT2) in 11, *SCN5A* mutations (LQT3) in 6, and *CACNA1C* (LQT8) in 1. Twelve patients also underwent genotyping, but no mutation was found. Table 2 lists the demographic and clinical features of these subjects (references 16, 17, and 23 reported the same cases 2, 12, and 27 in Table 2) and of those with no known mutations.

The remaining 17 subjects (6 fetuses, 8 neonates, 3 infants) did not undergo genetic analysis due to lack of such analysis at that time, death soon after birth, or refusal by parents. Five had SCD/ACA (Table 3), including a 1-day-old neonate who had AVB and died at 57 days of age in 1984. This case was later assumed to be LQT8, based on characteristic phenotypes such as syndactyly. AVB and VT/TdP were observed in 7 and 5 cases, respectively, in this group.

Although HR and QTc values were not different among LQT1, LQT2, LQT3, and mutation-negative groups, the incidence of VT/TdP was higher in LQT2 and LQT3 compared with LQT1 (Table 4). The incidence of AVB tended to be higher in LQT3 compared with LQT1 but statistically insignificant. On the other hand, the presence of family history of LQTS was more frequent in LQT1 than the mutation-negative group. The incidence of sinus bradycardia was comparable among the 4 groups (Table 4).

Table 3 lists cases with SCD/ACA; only 4 genetically confirmed cases were included, and 4 were mutation-negative, although the remaining 6 cases did not undergo genotyping. These individuals showed bradycardia (97±31 bpm; 10/14 showed HR <110 bpm) and markedly prolonged QTc (617±81 ms).

Treatment

With regard to the treatment of fetal VT/TdP, antiarrhythmic agents were administered transplacentally in 4 of 18 fetal cases (propranolol in 3 cases, lidocaine in 1, mexiletine in 1, flecainide in 1, and magnesium in 1), using the method described in detail in our previous report.[17] None of the 4 cases was genetically confirmed prenatally. When 2 or 3 of the following findings of sinus bradycardia, VT, and AVB were observed in a structurally normal heart, LQTS was strongly suggested, and β-blockers, sodium channel blockers (lidocaine, mexiletine), and magnesium (Mg) were selected as typical antiarrhythmic agents, instead of amiodarone or sotalol, which may prolong the QT interval. These drugs were used in combination until VT/TdP was controlled and proved effective in all 4 cases. However, preterm delivery was conducted in 2 cases both at 33 weeks of gestation due to recurrent VT/TdP and depression of fetal physical activity in one and to fetal hydrops and distress in the other. In the remaining 14 cases, pharmacotherapy was initiated after confirmation of the type of arrhythmias after birth. However, no fetal death was noted.

For 15 neonatal cases who presented with VT/TdP (including those who did not undergo genotyping), acute pharmacotherapy consisted of 2 or more of the following drugs: β-blockers, mexiletine, lidocaine, Mg, phenytoin, and others, except for 2 cases who were treated with phenytoin alone and 1 with mexiletine alone. Most of these cases were judged to respond the combination therapy. In 5 neonates in whom LQT3 was strongly suggested based on a typical ECG finding called late-appearing T wave, mexiletine was first administered but proved insufficient, and β-blockers were also added in all 5.

For those with LQTS presenting in infancy, 6 cases received acute pharmacotherapy (2 or all of propranolol, mexiletine, and Mg). No additional agent was administered. Thus, in all age groups, the acute therapy for VT/TdP consisted of a single drug to which 1 or more drugs was then added until the arrhythmia was controlled, independent of the genotype. Actually, the genotype was not identified during the acute phase in most cases. Furthermore, genotyping was not conducted in those 17 cases who presented before 1999.

Maintenance therapy consisted mainly of β-blockers (or no therapy) for LQT1 and mostly of mexiletine/β-blockers for LQT2 and LQT3 (Table 2). β-Blockers were added in 8 LQT2 cases after confirmation of the genotype. In all 6 LQT3 cases, mexiletine was maintained (combined with β-blockers) from acute through chronic phase after determination of the genotype.

Nine patients underwent pacemaker implantation (PMI), 5 with ventricular pacing mode (VVI) and 1 with atrial pacing mode (AAI), from age 1 day to 8 years due to severe bradycardia caused by AVB, inducing VT/TdP. In 6 cases, VT was completely suppressed after PMI. Only 2 patients had an implantable cardioverter-defibrillator (ICD) at ages 4 (LQT3) and 25 months (mutation negative), respectively, due to recurrent VT/TdP with satisfactory results.

Outcome

During the follow-up period of 8 days to 23.5 years (median, 4.25 years), 7 SCD and 7 ACA were registered (age at SCD or ACA range, 8 days to 10 years; median, 10.5 months); 6 did not have genetic testing, whereas 4 showed no mutation. Only 4 were genetically confirmed (Table 3). One case was later suspected to be LQT8, based on the phenotype including syndactyly. Among the 14 SCD/ACA cases, 12 had been under pharmacotherapy, 5 with both β-blockers and sodium channel blockers, and 2 had had PM or ICD. Four cases developed significant neurological deficits after cardiorespiratory resuscitation.

Discussion

The noteworthy finding of the present study was that 49 of 58 cases (84%) were diagnosed at the fetal or neonatal period, although this survey covered the entire infantile period. Remarkably, two thirds of the neonatal cases were diagnosed within 2 days of life; this period should be recognized as the most vulnerable period. The number of cases diagnosed after the neonatal period was only 9. Considering that the average age at appearance of symptoms in LQT2 and LQT3 is after

Table 2. Clinicogenetic Details

Case	LQT Type	Mutation	Age at Diagnosis/Sex	Clinical Presentation	FH	HR, bpm	QTc, ms
1	LQT1	Thr587Met	Fetus/M	FH, brady	+	109	561
2	LQT1	Ala341Val	Fetus/M	Brady	+	110	590
3	LQT1	Ala341Val	Neonate/M	FH	+	110	520
4	LQT1	Ile313Lys	Neonate/M	FH	+	102	589
5	LQT1	Ile313Lys	Neonate/M	FH	+	115	554
6	LQT1	276delSer	Neonate/M	Prolonged QT	+	115	570
7	LQT1	Asp611Tyr	Neonate/M	Brady	+	80	550
8	LQT1	Asp611Tyr	Neonate/F	FH	+	ND	ND
9	LQT1	Thr458Met	Neonate/M	FH	+	126	530
10	LQT1	Gly643Ser	Infant/M	ACA	−	109	554
11	LQT1	Gly269Ser	Infant/F	Cyanosis	−	113	586
					82%	109±12	560±24
12	LQT2	Gly628Ser	Fetus/M	VT/TdP, AVB	−	50	631
13	LQT2	del(7)(q32qter)	Fetus/F	TdP	−	111	492
14	LQT2	Ser243+112X	Fetus/F	FH	+	160	360
15	LQT2	Gly628Ala	Fetus/F	Syncope, VT/TdP, AVB	+	78	570
16	LQT2	Thr613Met	Fetus/M	VT/TdP, AVB	−	60	578
17	LQT2	Ala561Val	Neonate/M	Cyanosis, VT/TdP	−	86	520
18	LQT2	Gly628Ser	Neonate/M	TdP, brady	−	111	550
19	LQT2	Thr613Met	Neonate/M	convulsion, VT	−	140	599
20	LQT2	Gly572Ser	Neonate/F	TdP, AVB	−	91	520
21	LQT2	Ala614Val	Neonate/F	Syncope, VT	+	98	500
22	LQT2	Asn633Ser	Infant/F	VT/TdP, AVB	−	60	600
					27%	95±34	538±74
23	LQT3	Ala1186Thr	Fetus/M	AVB	+	78	679
24	LQT3	Asn1774Asp	Fetus/M	convulsion, VT/TdP, AVB	−	115	670
25	LQT3	Val176Met	Neonate/F	TdP, AVB	+	63	600
26	LQT3	Asn406Lys	Neonate/M	Syncope, TdP	+	129	598
27	LQT3	Arg1623Gln	Neonate/F	Heart failure	−	79	483
28	LQT3	Leu1772Val	Infant/M	ACA	−	138	520
					50%	100±31	592±79
29	LQT8	Gly406Arg	Neonate/M	AVB	−	141	581
30	Unidentified	−	Fetus/F	Brady	+	80	554
31	Unidentified	−	Fetus/M	Brady	−	100	510
32	Unidentified	−	Fetus/M	VT	−	85	590
33	Unidentified	−	Fetus/M	AVB	−	80	600
34	Unidentified	−	Neonate/F	Syncope	−	100	647
35	Unidentified	−	Neonate/F	Arrhythmia	−	126	586
36	Unidentified	−	Neonate/F	ACA	−	111	638
37	Unidentified	−	Neonate/M	Brady	−	93	550
38	Unidentified	−	Neonate/F	FH	+	120	520
39	Unidentified	−	Infant/F	ACA	−	160	470
40	Unidentified	−	Infant/F	ACA	−	100	774
41	Unidentified	−	Infant/F	PAC with block	−	60	460
					17%	104±32	575±86

(Continued)

Cases 2, 12, and 27 are reported in references 16, 17, and 23, respectively. ACA indicates aborted cardiac arrest; AVB, atrioventricular block; BB, β-blocker; brady, bradycardia; FH, family history; HR, heart rate; ICD, implantable cardioverter-defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death.

Table 2. Continued

Sinus Brady	VT/TdP	AVB	Acute Therapy	Maintenance Therapy	PMI/ICD	Follow-Up	Outcome
+	−	+	−	−	−	0 mo	Alive
+	−	−	−	BB	−	9 y	Alive
+	−	−	−	BB	−	4 y, 1 mo	Alive
+	−	−	−	BB	−	11 y, 10 mo	Alive
+	−	−	−	BB	−	10 mo	Alive
+	−	−	−	−	−	11 mo	Alive
+	−	−	−	−	−	7 y, 3 mo	Alive
+	−	−	−	−	−	5 y, 8 mo	Alive
−	−	−	−	−	−	4 y, 5 mo	Alive
+	−	−	Lido, Mexil	Mexil	−	9 y, 1 mo	Alive
+	−	−	−	−	−	7 y, 8 mo	Alive
73%	0%	9%				Median 68 mo	
+	+	+	Lido, Mg, BB, Mexil, Pacing	BB, Mexil	PM	3 y	Alive
+	+	−	−	BB	−	1 y	Alive
−	−	−	−	BB	−	2 y, 2 mo	Alive
+	+	+	Lido, Mg, BB, Mexil, pacing	BB, Mexil	PM	8 y, 1 mo	Alive
+	+	+	Mg, Mexil	BB, Mexil	−	8 mo	Alive
+	+	−	Lido, Mg, Mexil	BB, Mexil	−	11 y, 4 mo	Alive
+	+	+	Mexil	BB, Mexil	−	7 mo	Alive
−	+	−	Mg, BB	BB	−	8 y	Alive
+	+	+	Pheny	BB, Mexil	−	18 y, 5 mo	Alive
+	+	−	Pheny, DC	Pheny, BB	−	23 y, 6 mo	Alive
+	+	+	−	BB, Mexil	PM	15 y, 4 mo	Alive
82%	91%	55%				Median 96 mo	
+	+	+	Mexil	Mexil	PM ICD	3 y, 4 mo	Alive
+	+	+	BB, Mexil, Mg	BB, Mexil, Flecainide	PM	11 y, 4 mo	Alive
+	+	+	Lido, Mg, BB, Mexil	BB, Mexil	−	1 y, 3 mo	Alive
+	+	−	Lido, BB	BB, Mexil	−	11 mo	Alive
+	+	+	BB, Mexil, Lido	BB, Mexil	PM	8 y	Alive
−	+	+	Mg, BB, Mexil	BB, Mexil	−	3 y, 2 mo	Alive
83%	100%	83%				Median 39 mo	
−	+	+	BB, Mexil, Nifed	BB, Mexil, Nifed	−	3 y, 2 mo	Alive
+	−	+	−	BB, Mexil	−	2 y, 5 mo	Alive
+	−	−	−	BB	−	6 y, 5 mo	Alive
+	+	−	Lido, Mg	Mexil	−	5 y, 5 mo	Alive
+	−	+	BB, Mexil, Mg	BB, Mexil	−	4 mo	Alive
+	−	−	Lido, Mg, Isp	Mexil	−	4 y, 3 mo	Died
+	+	−	BB, Mg	BB	−	9 y, 5 m	Alive
−	+	−	Lido, BB, pheny, Mexil	Mexil	−	11 y, 9 mo	Alive
+	−	−	−	−	−	9 y, 6 mo	Alive
−	−	−	−	−	−	6 mo	Alive
−	+	−	BB, Mexil	BB, Mexil	ICD	7 y, 2 mo	Alive
+	+	+	Mexil	Mexil	−	4 y3 mo	Alive
+	−	−	BB, Mexil	BB, Mexil	−	7 y, 5 mo	Alive
75%	42%	25%				Median 71 mo	