A.

Borderline 4 Possible 2

Definite 29

C.

Asymptomatic 2

CPA 6

CHF 6

Arrhythmia 21

B.

(Y.O.)

50

25

0

Definite Borderline Possible

D.

(Y.O.)

50

25

0

*   *

CPA CHF arrhythmia asymptomatic

E.

(Y.O.)

50

25

0

#

*

CPA CHF arrhythmia

Figure 1. Characteristics of the probands. Number of the probands according to (**A**) diagnostic criteria and (**C**) first symptom. (**B,D,E**) Mean age at diagnosis according to (**B**) diagnostic category or (**D**) first symptom; and (**E**) at onset according to first symptom. CHF, congestive heart failure; CPA, cardiopulmonary arrest. *P<0.05, #P<0.01.

A. Dysfunction and structural alternations

10

24

1

B. Tissue characterization

3 3

29

C. Repolarization

8

4

23

D. Depolarization/conduction abnormalities

17

5

13

E. Arrhythmias

2

13

20

F. Family history

1

15

19

Figure 2. Number of the patients who fulfilled the criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia. Red, major criteria; blue, minor criteria; orange, none; light green, gene mutation carriers in major criteria.

Table 2. Desmosomal Gene Mutations Identified in the Present Study

No.	Sex	Age at diagnosis (years)	Category	PKP2		DSP		DSG2		DSC2	
				Codon	Amino acids	Codon	Amino acids	Codon	Amino acids	Codon	Amino acids
1	M	30	Definite	1725–1728dupGATG	R577DfsX5						
2	M	49	Definite								
3	M	16	Definite	1132 C>T	Q378X						
4	F	36	Definite								
5	M	51	Definite								
6	F	15	Definite							394 C>T	R132C
										582 C>G	N194K
										607 C>T	R203C
7	M	64	Definite								
8	F	15	Definite			8269 G>C	D2757H				
9	M	49	Definite			2360 A>G	Y787C				
10	F	47	Definite	2150 C>T	P717L†						
11	M	72	Definite	953 A>C	H318P†						
12	M	45	Definite								
13	M	40	Definite			4741 A>G (H)	K1581E† (H)	1592 T>G	F531C		
14	M	41	Definite	976 G>A (H)	A326T† (H)	593 A>C (H)	Q198P (H)				
15	F	16	Borderline			8455 A>C	M2819L†				
16	M	5	Definite								
17	M	17	Definite	1725–1728dupGATG	R577DfsX5						
18	M	38	Definite								
19	F	25	Borderline								
20	F	63	Possible								
21	M	43	Definite								
22	M	30	Borderline								
23	M	32	Borderline								
24	F	47	Definite								
25	M	70	Definite								
26	F	18	Possible					2780 C>T	P927L#		
27	M	56	Definite	875–890 del	L266QfsX104						
28	F	43	Definite					1481 A>C	D494A† (H)		
29	M	25	Definite	2119 C>T	Q707X						
30	F	63	Definite								
31	M	56	Definite					1481 A>C	D494A†		
32	M	50	Definite			4741 A>G	K1581E†				
33	M	34	Definite	2095 C>T	Q699X			2780 C>T	P927L#		
34	M	62	Definite			1203 G>T	K401N				
35	F	53	Definite	1725–1728dupGATG	R577DfsX5						

†Reported in NCBI SNP database; #identified in the present control cohort. H, homozygous mutation.

healthy Japanese controls.

Age Analysis

The present probands were divided into 2 groups according to age at diagnosis: ≤40 years old (younger group, n=16) and >40 years old (older group, n=19). We also compared the clinical and genetic characteristics between the 2 groups.

Statistical Analysis

All continuous variables are reported as mean±SD. Differences between continuous variables were evaluated using the Wilcoxon rank sum test for 2 groups and 1-way ANOVA for ≥3 groups. Categorical variables were analyzed using chi-square test (for counts ≥5) or Fisher exact test (for counts <5) for 2 groups and Kruskal-Wallis ANOVA rank test for >2 groups. Significance was considered at P<0.05.

Results

Clinical Features

Clinical subject characteristics are summarized in **Table 1**. According to the 2010 diagnostic ARVC/D criteria,[18] 29 probands
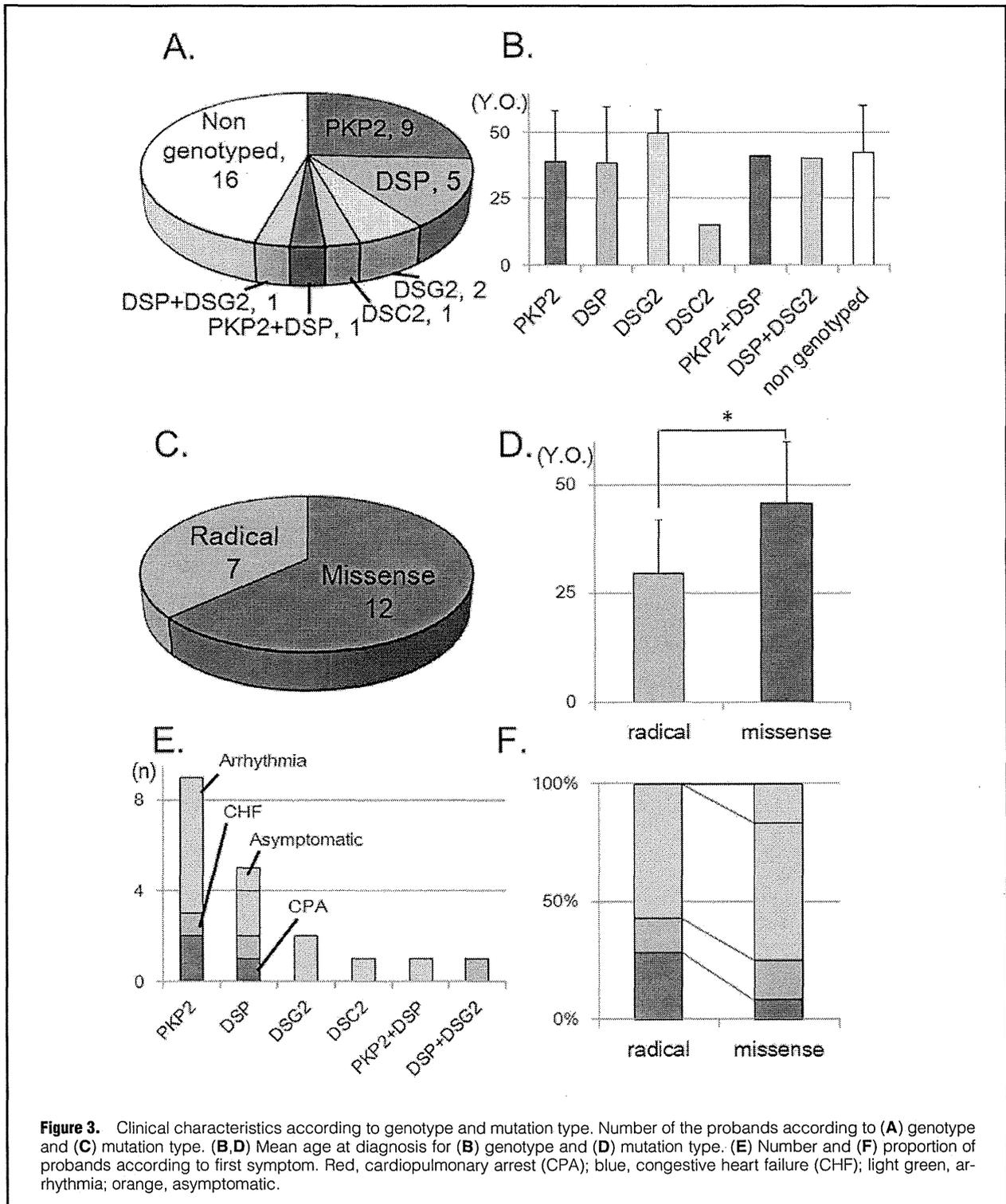
Figure 3. Clinical characteristics according to genotype and mutation type. Number of the probands according to (**A**) genotype and (**C**) mutation type. (**B,D**) Mean age at diagnosis for (**B**) genotype and (**D**) mutation type. (**E**) Number and (**F**) proportion of probands according to first symptom. Red, cardiopulmonary arrest (CPA); blue, congestive heart failure (CHF); light green, arrhythmia; orange, asymptomatic.

(82.9%) were diagnosed as definite, 4 (11.4%) as borderline, and 2 (5.7%) as possible (**Figure 1A**). The mean age at diagnosis was 40.5±17.7 years. They experienced their first symptoms at 38.6±14.8 years, although 2 probands were diagnosed with ARVC/D without symptoms. The asymptomatic probands first consulted doctors due to ECG abnormality, and

were diagnosed with ARVC/D. Mean age at diagnosis in each diagnostic category was not significantly different: 42.5±17.4 years in the definite group, 25.8±7.1 years in the borderline group, and 40.5±31.8 years in the possible group (**Figure 1B**).

Figure 1C summarizes the number of probands according to first symptom, and **Figures 1D,E**, the mean age at diagnosis

Table 3. Subject Characteristics vs. Age at Diagnosis			
	Younger group (n=16)	Older group (n=19)	P-value
Age at onset (years)	24.4±9.5	48.9±7.5	<0.001
Age at diagnosis (years)	24.5±10.2	53.9±9.4	<0.001
Initial manifestation			
Cardiac arrest	5 (31.3)	1 (5.3)	0.073
Arrhythmia	7 (43.8)	14 (73.7)	0.146
Heart failure	2 (12.5)	4 (21.1)	0.666
Asymptomatic	2 (12.5)	0 (0)	0.202
ARVC/D diagnostic criteria			
Definite	11 (68.8)	18 (94.7)	
Borderline	4 (25)	0 (0)	0.333
Possible	1 (6.3)	1 (5.3)	
Desmosomal mutations			
All	9 (54.2)	10 (52.6)	0.899
PKP2	5 (31.3)	4 (21.1)	0.656
PKP2 radical	5 (31.3)	2 (10.5)	0.17
DSP	2 (12.5)	3 (15.8)	1
DSG2	0 (0)	2 (10.5)	1
DSC2	1 (6.3)	0 (0)	0.474
DSP+DSG2	1 (6.3)	0 (0)	0.474
PKP2+DSP	0 (0)	1 (5.3)	1

Data given as mean±SD or n (%). ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia.

and onset. Probands whose first symptom was cardiopulmonary arrest (CPA) were significantly younger than those whose first symptom was arrhythmia or congestive heart failure. The mean age at onset and diagnosis in the CPA patients were 22.3±15.3 years and 22.7±15.6 years, respectively.

Letters A and I in **Table 1** indicate the presence of positive major and minor criteria by the revised task force,[18] respectively. In **Table 1**, diagnostic criteria are also summed with the result for the diagnostic category. Regarding the RV dysfunction and structural alterations criteria, 24 probands (68.6%) fulfilled major criteria and 1 (2.9%) a minor criterion (**Figure 2A**). Regarding endocardial biopsy, only 3 probands fulfilled major and 3 minor criteria because tissue characterization from the RV free wall was not available in most cases (**Figure 2B**). Eight probands (22.9%) fulfilled criteria for major repolarization abnormalities and 4 (11.4%) minor criteria (**Figure 2C**). Epsilon waves were observed in 5 (14.3%), and 13 (37.1%) had other depolarization abnormalities (**Figure 2D**). In 33 probands (94.3%), ventricular tachycardia (VT) or frequent premature ventricular contraction (PVCs) were documented; in 13 of them (37.1%), VT with both a superior axis and left bundle-branch morphology was observed (**Figure 2E**). Only 1 proband (no. 25) had a clear family history of ARVC/D in first-degree relatives, and 19 (54.3%) were found to carry pathogenic mutations in at least 1 gene of desmosomal proteins (M, **Table 1**) and, therefore, fulfilled family history criteria (**Figure 2F**).

Genetic Testing

We identified ARVC/D-related gene variants in 19 probands (**Table 2**). No variants except DSG2-P927L (indicated by #) were identified in the 200 control alleles. Because DSG2-P927L was identified in 1 control as a heterozygote, we classified this variant (probands 26 and 34) as a bystander single-nucleotide polymorphism (SNP). Three of them carried compound or digenic mutations. Mutations indicated by (H)

in **Table 2** were homozygous, and those indicated by † are rare variants according to the National Center for Biotechnology Information (NCBI) SNP database.

Figure 3A shows the numbers of carriers of each gene mutation, and **Figure 3B** the mean age at diagnosis according to genotype, which was not significantly different. PKP2 mutations were identified in 10 probands (28.6%). Seven of them carried radical mutations that caused an inappropriate termination of the protein (**Figure 3C**). DSP and DSG2 mutations were all missense and were identified in 7 (20.0%) and 3 (8.6%) probands, respectively. One proband (no. 6) carried 3 DSC mutations. The mean age at onset was not significantly different between mutation carriers (39.1±15.5 years) and non-carriers (37.9±14.5 years). Concerning the probands with radical mutations (**Figure 3D**), onset was significantly younger (29.4±12.4 years) than in those with missense mutations (45.8±14.2 years; P=0.0266). **Figure 3E** summarizes first symptom according to gene mutation. Three of 6 patients who suffered CPA carried mutations in PKP2 or DSP. Regarding the mutation type (**Figure 3F**), 2 patients (28.6%) with radical mutations suffered CPA; in contrast, only 1 (8.3%) with a missense mutation did. Two asymptomatic patients carried missense mutations.

Age, and Clinical and Genetic Characteristics

Development of the disease seems to be different between young and older patients, and the mean age at diagnosis in the present cohort was approximately 40 years old. Therefore we divided the present cohort into 2 groups according to this age and compared clinical and genetic characteristics (**Table 3**). Regarding initial clinical manifestation, 31.3% patients suffered cardiac arrest in the younger group, whereas 5.3% did, in the older group. In contrast, 2 asymptomatic probands belonged to the younger group. Four probands in the younger group were diagnosed as having borderline ARVC/D, whereas none had this in the older group.

Table 4. Clinical and Mutation Characteristics of Family Members							
Family no.	Subject no.	Age at diagnosis (years)	Sex	Diagnosis			Mutations
				Major criteria	Minor criteria		Amino acids
3	**1**	16	M	3	1	Definite	PKP2 Q378X
	2	?	M	1		Possible	(–)
	3	?	F	1		Possible	(–)
	4	?	F	1		Possible	(–)
4	1	36	F	2	1	Definite	(–)
	2	11	F	1		Possible	(–)
	3	13	F	1		Possible	(–)
6	**1**	15	F	2	2	Definite	DSC R132C N194K R203C
	2	?	F	1		Possible	DSC N194K R203C
	3	12	M	1		Possible	(–)
13	1	40	M	2	2	Definite	DSP K1581E*(H) DSG2 F531C
	2	76	M	1		Possible	DSP K1581E* DSG2 F531C
	3	66	F	1		Possible	DSP K1581E*
17	**1**	17	M	3	1	Definite	PKP2 R577DfsX5
	2	20	M	3		Definite	PKP2 R577DfsX5
18	1	38	M	1	2	Definite	(–)
	2	7	M	1		Possible	(–)
28	**1**	43	F	3		Definite	DSG2 D494A*
	2	56	M	2		Definite	DSG2 D494A*
	3	23	M	1		Possible	DSG2 D494A*
	4	14	F	1		Possible	DSG2 D494A*
31	1	56	M	2	2	Definite	DSG2 D494A*
	2	61	F	2	1	Definite	DSG2 D494A*
	3	26	F	1		Possible	(–)

Bold, Proband. *Reported in NCBI SNP database.

Desmosomal gene mutations were identified in 9 probands from the younger group and in 10 from the older group. There was no difference in the number of mutation carriers of the respective genes. Five probands from each group carried *PKP2* mutations, but the number of radical *PKP2* mutation carriers was higher in the younger (n=5) than the older (n=2) group.

Family Members

We examined 16 family members from 8 families, and identified desmosomal gene mutations in 8 members from 6 families (**Table 4**). Only 3 of them satisfied the diagnostic criteria for definite ARVC/D and they were all found to have desmosomal gene mutations. A 20-year-old man with a definite diagnosis (subject 17-2) remained asymptomatic without treatment. In contrast, 2 other family members with a definite diagnosis (28-2 and 31-2) were a 56-year-old man and a 61-year-old woman, and both were symptomatic and receiving treatment. The remaining family members were diagnosed in the possible category because first-degree relatives fulfilled the major criteria of family history.

Discussion

In this study, we first performed a comprehensive examination of 35 Japanese ARVC/D patients and their 16 family members. Furthermore, we analyzed the age-dependent clinical and genetic features of the ARVC/D patients.

Age-Dependent Features

In the clinical course of ARVC/D, it is well-known that patients become symptomatic at around 40.[15,16] Because the disease displays a dominant or recessive inheritance trait, we can examine the family members after the diagnosis of the probands. Advances in molecular genetics facilitated the early detection of ARVC/D before disease onset not only for possible probands, but also their family members. In contrast, however, sporadic cases were rarely diagnosed before onset. As described here, 5 young patients suffered from cardiac arrest as the first symptom. Also, in the present cohort, 2 young patients were diagnosed before onset of symptoms due to ECG abnormalities recorded in a health check-up at high school. One had frequent PVCs and another had T-wave inversion in the right precordial leads.

Corrado et al described the age dependence of the disease with regard to the clinicopathology.[21] They analyzed 42 whole hearts of patients with a pathologic diagnosis of ARVC/D at postmortem examination or after heart transplantation. According to the left ventricular (LV) involvement, the patients were classified into 3 groups. Consequently, they reported that the group with LV involvement was significantly older than the others and had highly developed heart failure. This agrees with the present finding of the patients whose onset was heart failure being older than those who developed cardiac arrest. Concerning the unexpected sudden cardiac death, 200 of 1,930 autopsy subjects were diagnosed as having ARVC/D.[22] In that report, there was a gradual increase of sudden cardiac death until the late 30 s, followed by a progressive decrease.

In a recent study involving 53 pediatric ARVC/D patients with desmosomal mutations,[17] only 40% of mutation carriers fulfilled the diagnostic criteria. The frequency of ECG abnormality in genotyped patients, however, was significantly higher in probands than in family members; 12 of 13 probands in that study had ECG abnormality.[17] Taken together, ECG in adolescence would be effective for the early diagnosis of ARVC/D, as well as the prevention of sudden cardiac death. In Japan, ECG is obligatory in schools at the age of 6, 12, and 15 years. Therefore, we can identify abnormal ECG carriers, and further examine their cardiac function to prevent unexpected cardiac sudden death.

Although there was no age dependence in each gene mutation carrier, carriers with *PKP2* radical mutations developed the disease at a significantly younger age than other mutation carriers (**Figure 3D**). This implies that nonsense or frameshift mutations may cause severer phenotypes and the early onset of ARVC/D, because multiple desmosomal mutations cause earlier onset and more severe phenotype.[16,23] In **Table 3**, we could not identify the clear clinical and genetic differences between younger and older groups, but we should bear in mind that the onset in the younger ARVC/D patients might be CPA, as shown in **Figures 1D,E**.

Desmosomal Mutations in Japan

Kapplinger et al reported desmosomal gene mutations identified in healthy controls in comparison with ARVC/D patients.[24] They reported that missense mutations in *DSP* and *DSG2* were frequently identified in non-Caucasian controls. Concerning the desmosomal variant, Fressart et al used software to distinguish whether the variants were disease-causing mutations or genetic variants of unknown significance.[16] In the present cohort, we identified 2 *DSG2*-P927L carriers in the healthy controls. Also, 5 desmosomal variants we found were reported in the NCBI SNP database. It was, however, difficult to distinguish whether the variants were benign or not, because the healthy controls might develop the disease at a later date. Concerning the family members, only 3 of 8 with gene mutations fulfilled the criteria for definite ARVC/D. Originally, the penetrance of the disease with *PKP2* mutations was reported to be very low.[3,8,25] As the reason for low penetrance, additional genetic or environmental factors, including age, might affect the onset of the disease. Therefore, we need to perform careful follow-up of the genotyped family members to elucidate the effect of the variants on the progression of the disease, especially in young carriers.

Study Limitations

The number of ARVC/D patients in the present study was limited to 35, and this number was smaller than in other studies reported from Europe and the USA. Because we did not screen for *JUP*, the present mutation-negative patients may have carried mutations of *JUP*.

Conclusions

In Japan, as reported in Western countries, *PKP2* mutations are the major cause of ARVC/D among desmosomal genes. In young patients, fatal arrhythmias and cardiac arrest are sometimes the first symptom; therefore, the identification of genetically affected family members, especially those with *PKP2* mutations causing a premature stop codon, is indispensable for preventing sudden death.

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Drug-induced QT-interval prolongation and recurrent torsade de pointes in a child with heterotaxy syndrome and *KCNE1* D85N polymorphism [☆],[☆☆]

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Abstract

We present a child case of heterotaxy syndrome (asplenia syndrome) after Fontan procedure that showed extreme prolongation of QT interval and torsade de pointes (TdP) after administration of sodium channel blockers for paroxysmal atrial tachycardia. Despite low serum concentration of the drugs, QT prolongation persisted and TdP attacks with unconsciousness recurred, possibly in association with junctional bradycardia and myocardial damage although he had never experienced QT prolongation during bradycardia before. Temporal cardiac pacing via a venous route to exclude possible implication of bradycardia in induction of TdP was difficult to apply due to total cavopulmonary connection (TCPC) circulation. Continuous intravenous administration of low-dose isoproterenol was started but an appropriate heart rate for prevention of TdP was difficult to obtain. Finally, we were urged to conduct implantation of a DDD pacemaker combined with ICD surgically with epicardial leads, resulting in successful suppression of TdP and syncope. Screening of the genotype disclosed the *KCNE1* D85N polymorphism, which is known as one of the typical disease-causing gene variants in long-QT syndrome (LQTS).
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Keywords: Drug-induced long-QT syndrome; Torsade de pointes; *KCNE1* D85N; Sodium channel blocker

Introduction

Antiarrhythmic agents are known to potentially cause QT-interval prolongation and torsade de pointes (TdP), i.e., drug-induced long-QT syndrome (di-LQTS). Recent advancements in molecular biology have revealed that genetic background is often implicated in this life-threatening proarrhythmia.[1] Here, we present a child case of heterotaxy syndrome (asplenia syndrome) after Fontan procedure that showed extreme prolongation of QT interval and recurrent TdP after administration of sodium channel blockers for paroxysmal atrial tachycardia. Screening of the genotype disclosed the *KCNE1* D85N polymorphism, which is known as one of the typical disease-causing gene variants in LQTS.[2]

Case report

A 15-year-old boy was admitted to our hospital because of palpitations. The patient had been diagnosed with heterotaxy syndrome, single atrium, double-inlet single ventricle, pulmonary arterial stenosis, and total anomalous pulmonary venous return (TAPVR), and had undergone total cavopulmonary connection (TCPC) with an extra cardiac conduit combined with TAPVR repair. Electrocardiogram (ECG) on admission revealed atrial tachycardia (AT) with 1:1 atrioventricular conduction (heart rate 150 bpm) although the patient had not previously shown significant arrhythmias, except for transient asymptomatic junctional or sinus bradycardia probably associated with heterotaxy with a heart rate of around 50–60 bpm (Fig. 1). He was hemodynamically stable and medical therapies were started. Repeated intravenous injections of ATP (maximum dose, 0.25 mg/kg) and procainamide (5 mg/kg) failed to convert AT into sinus rhythm. Then, intravenous disopyramide (1 mg/kg) was administered. Eight minutes after the infusion, pulseless tachycardia was suddenly provoked, and a DC shock was applied, resulting in successful conversion. However, AT recurred shortly and therefore continuous infusion of low doses of landiolol (3 µg/kg/min)
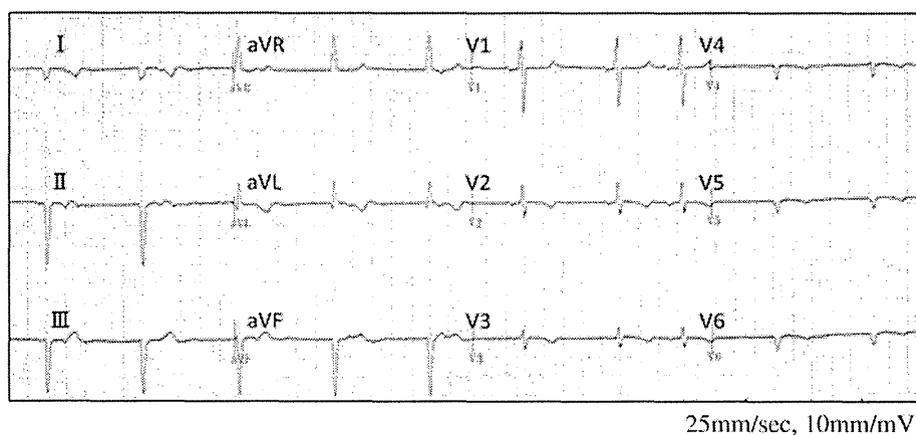
25mm/sec, 10mm/mV

Fig. 1. Baseline 12-lead ECG recorded 3 months before admission, showing junctional bradycardia with a normal QT interval (heart rate 60 bpm, QTc 400 ms).

and digoxin (0.005 mg/kg, twice a day) were started, in order to control the heart rate and to prevent circulatory collapse by recurrence of AT/tachycardia. AT was then under controlled but bradycardia developed gradually and remarkable QT-interval prolongation (QTc ≥ 580 ms) with frequent premature ventricular contraction appeared on ECG monitoring (Fig. 2A and B). Serum levels of potassium, calcium and magnesium were all normal. Although all antiarrhythmic drugs were discontinued, extreme QT prolongation persisted and TdP attacks with unconsciousness recurred (Fig. 2C), necessitating DC shocks several times.

Because immediate application of temporal cardiac pacing via a venous route to exclude possible implication of bradycardia in induction of TdP was difficult to apply due to TCPC circulation, we tried continuous intravenous administration of low doses of isoproterenol. However, an appropriate heart rate for the prevention of TdP was difficult to obtain and a storm of TdP attacks reoccurred. Serum concentration of both procainamide and disopyramide later turned out to be low (0.7 and 0.3 μg/ml at 12 h and 0.5 and, <0.1 μg/ml at 36 h after administration, respectively) compared with their therapeutic ranges (4–10 and 2.8–3.2 μg/ml, respectively). Ultimately, 60 h after admission, we were urged to conduct implantation of a DDD pacemaker combined with ICD surgically with epicardial leads, resulting in successful suppression of TdP and syncope.

A genetic test for LQTS candidate genes revealed the KCNE1 D85N polymorphism in the index case and in his father (Fig. 3). His mother was negative for the single nucleotide polymorphism (SNP).

Discussion

The present case demonstrated that, even with low serum concentration of sodium channel blocker, marked QT prolongation and recurrent TdP can occur if the patient has other coexistent predisposing factors such as polymorphisms in the LQTS-related genes, as well as bradycardia. Ackerman et al.[3] reported that the allele frequency of the KCNE1 D85N polymorphism, which was detected in the present case, is approximately 0.7% in healthy Asian populations. According to the survey conducted by Nishio et al.[2] in Japan, its

frequency among LQTS probands (3.9%) is significantly higher than that in healthy control subjects (0.81%). This gene polymorphism has recently gathered much interest as a typical culprit of unexpected sudden cardiac death or aborted cardiac death as well as di-LQTS.[4] In an experiment using Xenopus oocytes, I_{Ks} currents were reduced by approximately 50% under heterologous expression of the D85N gene variant.[5] Another functional analysis study using hamster ovarian cells showed that I_{Ks} and I_{Kr} currents of those with the D85N gene variant were reduced by 28% and 31%–36%, respectively.[2]

Sodium channel blocker is one of the most common antiarrhythmic agents used for treatment of tachyarrhythmias. On the other hand, it is also known as one of the typical drugs that provoke di-LQTS/TdP.[1] Sodium channel blocker prolongs both myocardial depolarization and repolarization especially in ischemic or injured regions, enhancing electrical dispersion of myocardium. In the present case, it is difficult to conclude that the significant QT-interval prolongation was caused by KCNE1 D85N alone. Implication of heterotaxy-related junctional or sinus bradycardia at baseline or some kind of myocardial damage such as clinically unapparent myocarditis in the development of LQT/TdP could not be fully excluded. However, it is unlikely that the latter mechanism alone induced LQT/TdP because the patient had never shown prolonged QT or symptomatic arrhythmias previously even during the phase of marked bradycardia or hemodynamic instability around surgical procedure. It is considered reasonable that KCNE1 D85N played a significant role as genetic background for development of the life-threatening event in this patient. However, this genetic variance does not seem to have any pathophysiologic relevance to heterotaxy syndrome because we are not aware of any case reports that indicate such association in the literature.

It should be noted that a transvenous approach for temporal pacing is not easy in patients with complex heart disease who have already undergone TCPC in spite of the fact that heterotaxia hearts are often complicated by supraventricular tachycardia, necessitating the use of anti-tachycardia drugs.[6] If a patient with heterotaxy shows episodes of sustained tachycardia, electrophysiological study and catheter ablation of the foci of tachycardia, if necessary, should be conducted before Fontan procedure.
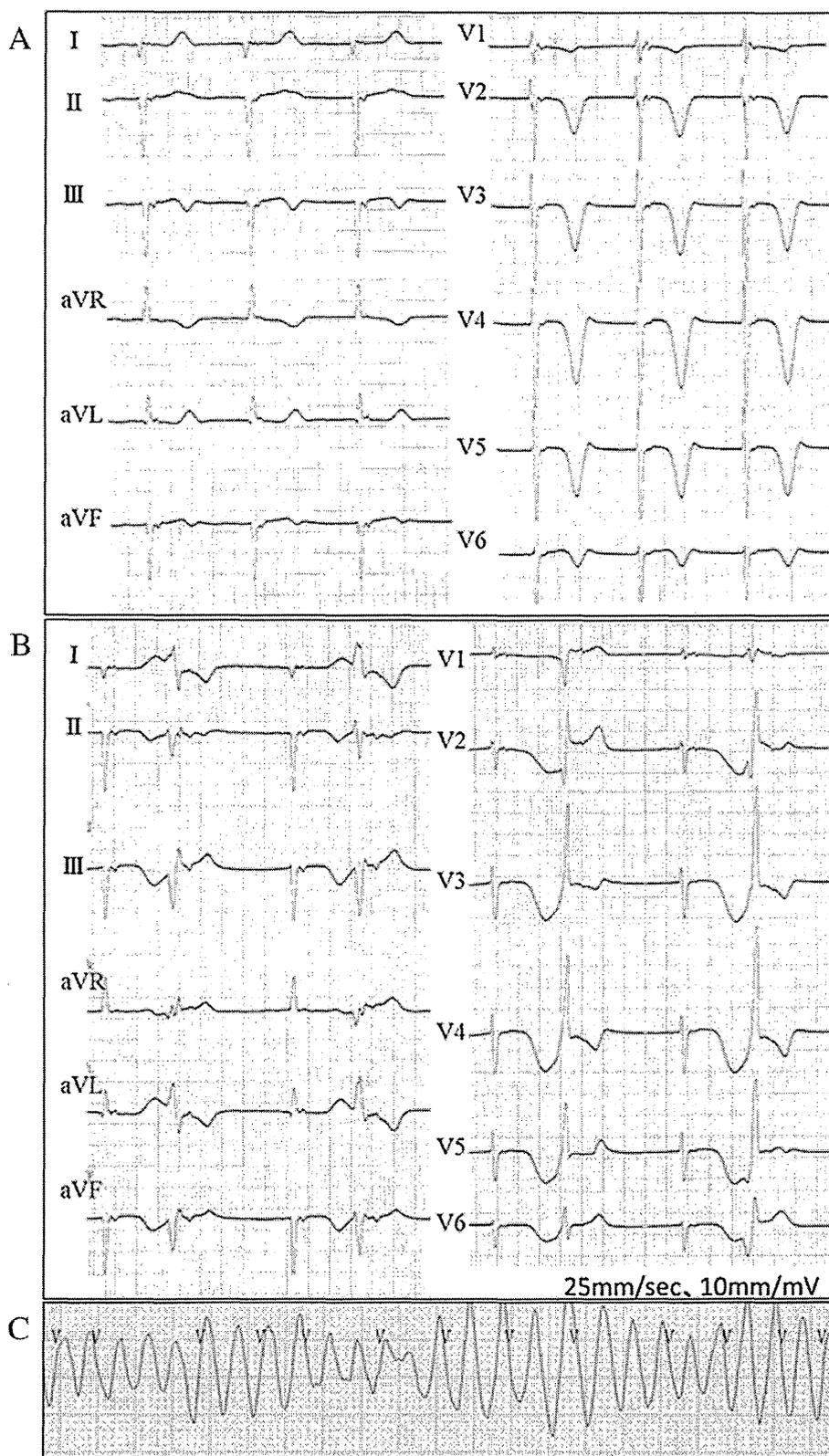
Fig. 2. A: ECG recorded 11 h after administration of sodium channel blockers, showing marked QT-interval prolongation with bradycardia (heart rate 60 bpm, QTc 580 ms). B: ECG showing marked QT-interval prolongation and bigeminy of premature ventricular contraction. C: TdP following extreme QT prolongation.
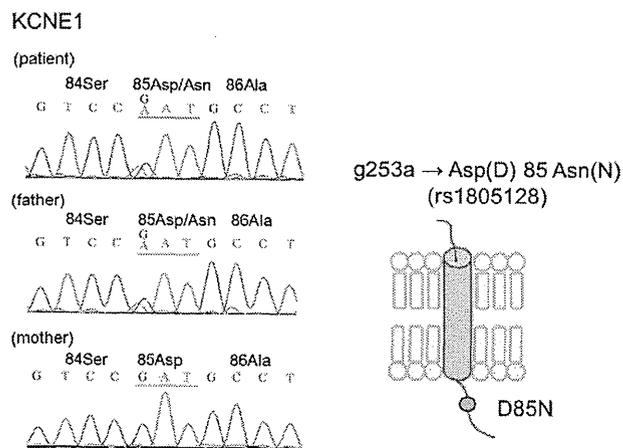
KCNE1

Fig. 3. Representation of direct sequencing of the *KCNE1* of the patient and parents. A G to A transition at codon 253 and resultant amino acid substitution of asparagine for aspartic acid were detected in the index patient and father.

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Clinical and electrocardiographic characteristics of patients with short QT interval in a large hospital-based population

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BACKGROUND Short QT syndrome is one of the underlying disorders associated with ventricular fibrillation. However, the precise prognostic implication of a short QT interval remains unclear.

OBJECTIVE The purpose of this study was to investigate the prevalence and long-term prognosis in patients with a shorter-than-normal QT interval in a large hospital-based population.

METHODS We chose patients with a short Bazett QTc interval from a database consisting of 114,334 patients to determine the clinical characteristics and prognostic value of a short QT interval.

RESULTS A total of 427 patients (mean age 43.4 ± 22.4 years) had a short QT interval with about a 1.2 times higher male predominance (234 men). The QTc interval was significantly longer in female than in male patients (363.8 ± 6.1 ms vs 357.1 ± 5.8 ms, $P <.0001$). The age-specific prevalence of patients with short QT interval was biphasic, peaking at young and old age. Atrial fibrillation and early repolarization were complicated with short QT interval in 39 (9.1%) and 26 (6.1%) patients, respectively. The prognosis of 327 patients (182 men; mean age, 46.4 ± 27.3 years)

with a short QT interval could be assessed (mean follow-up period, 54.0 ± 62.0 months). During the follow-up, 2 patients, 1 of whom had early repolarization, developed life-threatening events, in contrast to 6 patients who died of noncardiac causes and did not have early repolarization.

CONCLUSION The prevalence of a short QT interval showed a slight male preponderance and biphasic age-dependent distribution in both genders. The complication rate of atrial fibrillation was higher in those with a short QT interval than in general populations. The long-term outcome suggested that early repolarization in a short QT interval might be associated with potential risk of lethal arrhythmia.

KEYWORDS Electrocardiography; QT interval; Prevalence; Prognosis; Repolarization

ABBREVIATIONS AF = atrial fibrillation; **CI** = confidence interval; **ECG** = electrocardiogram

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Introduction

The QT interval is an invaluable prognostic marker for evaluating whether ventricular arrhythmia occurs.[1–3] Long QT syndrome is characterized by ventricular cells that fail to repolarize sufficiently quickly. On the other hand, short QT syndrome manifests an extremely abbreviated QT interval.[4,5] Genetic mutations underlie both syndromes, in which sudden cardiac death occurs.[6,7] It was reported that short QT syndrome complicated other electrocardiogram (ECG) abnormalities, such as atrial fibrillation (AF)[4] and early repolarization.[8] Although close attention must be paid

to short QT interval, there may be overlap between normal QT interval and abnormally short QT interval.[9] In addition, the prognostic value of short QT syndrome in relation to AF or early repolarization is yet to be determined.

In our university hospital, more than 350,000 ECGs obtained from more than 110,000 patients are available for digital analysis. Using this large hospital-based population, we aimed: (1) to determine the distribution of the QT interval in the entire population, (2) to determine the clinical and ECG characteristics in individuals with short QT interval, and (3) to investigate the prognostic value of short QT interval.

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Methods

The research protocol was approved by the Ethical Committee of Shiga University of Medical Science.

Database

We analyzed resting 12-lead ECGs recorded in the university hospital of Shiga University of Medical Science. The 114,334 consecutive patients (55,091 female and 59,243 male patients) who had undergone ECG recordings between January 1983 and July 2010 were enrolled in the present study. A total number of 359,737 ECG recordings were obtained during this period. The 12-lead ECG was recorded for 10 seconds at a sweep speed of 25 mm/s, calibrated to 1 mV/cm in the standard leads. Twelve leads were simultaneously acquired. The ECG signals were recorded with a temporal sampling interval of 2 ms (i.e., 500 Hz). Digital data were stored in a server computer with 12-bit resolution.

Digital analysis of ECG

MUSE7.1 (GE Marquette Medical Systems, Inc., Milwaukee, Wisconsin) detected an identical P wave and QRS complex with a template matching technique. When AF (defined as irregular RR intervals with fibrillatory waves) was present, only QRS complex was identified by template-matching technique. ECG variables measured were composed by the averaged value during a 10-second recording time. QT interval was measured from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of repolarization in any lead (T wave offset). T wave offset was determined by the time when 98% of the integrated area of T wave was over, which corresponded to a point where the T wave downsloping limb nearly joined the baseline. U wave was excluded. The QTc interval was calculated after correction for heart rate with the Bazett formula. Early repolarization was defined as an elevation at the junction between QRS complex and ST-segment ≥0.1 mV from baseline level in at least 2 leads. ST-segment elevation should be present in at least 2 consecutive beats to identify early repolarization. ECG recordings of a mean heart rate <50 or >100 beats/min were excluded from the analysis in the first analysis, and then the prevalence of short QT interval in patients with sinus bradycardia <50 beats/min was additionally investigated. ECGs with ventricular pacing were also excluded. Because all measurements of 12-lead ECG were digitally performed by virtue of software, neither intraobserver nor interobserver variability occurred in this study. To determine whether the automatic measure of QT interval correlates with the manual measure of QT interval, 1,000 ECGs were randomly selected, and then we compared the automatic and manual measure of the QT interval. The manual measure of the QT interval was performed by a standard tangential method in lead V5. The manual QT interval measurement was obtained by averaging the QT interval of 3 consecutive beats.

Data analysis

First, we constructed histograms according to QTc interval. QTc interval divided by 5 ms and the number of ECGs or patients used for frequency density were shown on the abscissa and the ordinate, respectively. Second, the prevalence of patients with a short QTc interval in association

with age and gender was determined. Third, clinical and ECG characteristics of patients with a short QTc interval were determined. The prevalence of AF and early repolarization complicated by short QT interval was determined. Fourth, the prognostic value of a short QTc interval was assessed. Long-term outcome was determined by assessing whether sudden cardiac death, life-threatening ventricular arrhythmia, or any cause of death occurred. Patients were considered to have died suddenly if death was observed and had occurred within 1 hour after new or more serious complaints of probable cardiovascular cause. Life-threatening ventricular arrhythmia was determined by documented ECG. We reviewed the medical records of patients with short QT interval to evaluate their physical health status. In patients whose medical records were not available to determine prognosis, we gathered information on health status by a postal questionnaire. We performed gene analysis (see Supplementary Materials) in patients who developed life-threatening events with short QT interval.

Statistical analysis

The data are presented as mean ± SD. A comparison between 2 groups was performed with the Student t test or the nonparametric Mann-Whitney U test, as appropriate. Categorical variables were compared with χ^2 test. Kolmogorov-Smirnov test was performed to determine whether QTc interval distribution fit to a normal distribution. All tests were 2-tailed, and a value of $P < .05$ was considered statistically significant.

Results

In the database, there were 11,416 and 21,450 ECGs with heart rate of <50 and >100 beats/min, respectively. We excluded these ECGs from this study, thus 301,345 ECGs derived from 105,824 patients (56.0% men; mean age, 52.6 ± 20.7 years) were included for the analysis of this study. The autonomic QT interval measure was a little but significantly longer than the manual QT interval measure (421.8 ± 23.2 ms vs 418.0 ± 24.5 ms, $P < .0001$).

The mean difference between the manual and automatic QT interval measure was 3.8 ms (median 3.7 ms), and there was a significant linear correlation (r = 0.95, $P < .00001$) between the manual and autonomic measure of QT interval (Supplementary Figure 1), indicating the accuracy of the computer-assessed measure of QT interval.

Prevalence of QT interval

Figure 1 shows the distribution of the QTc intervals of total, male, and female patients. The histograms that were constructed as a function of the number of ECGs are shown in the upper row of Figure 1. The mean QTc interval was 421.4 ± 25.7 ms (95% confidence interval [CI] 382 to 482 ms, range 329 to 693 ms) in total patients; 418.9 ± 25.7 ms (95% CI 380 to 480 ms, range 331 to 693 ms) in male patients; and 424.7 ± 25.3 ms (95% CI 387 to 483 ms, range 329 to 687 ms) in female patients. The QTc interval was significantly ($P < .0001$) longer in female patients than
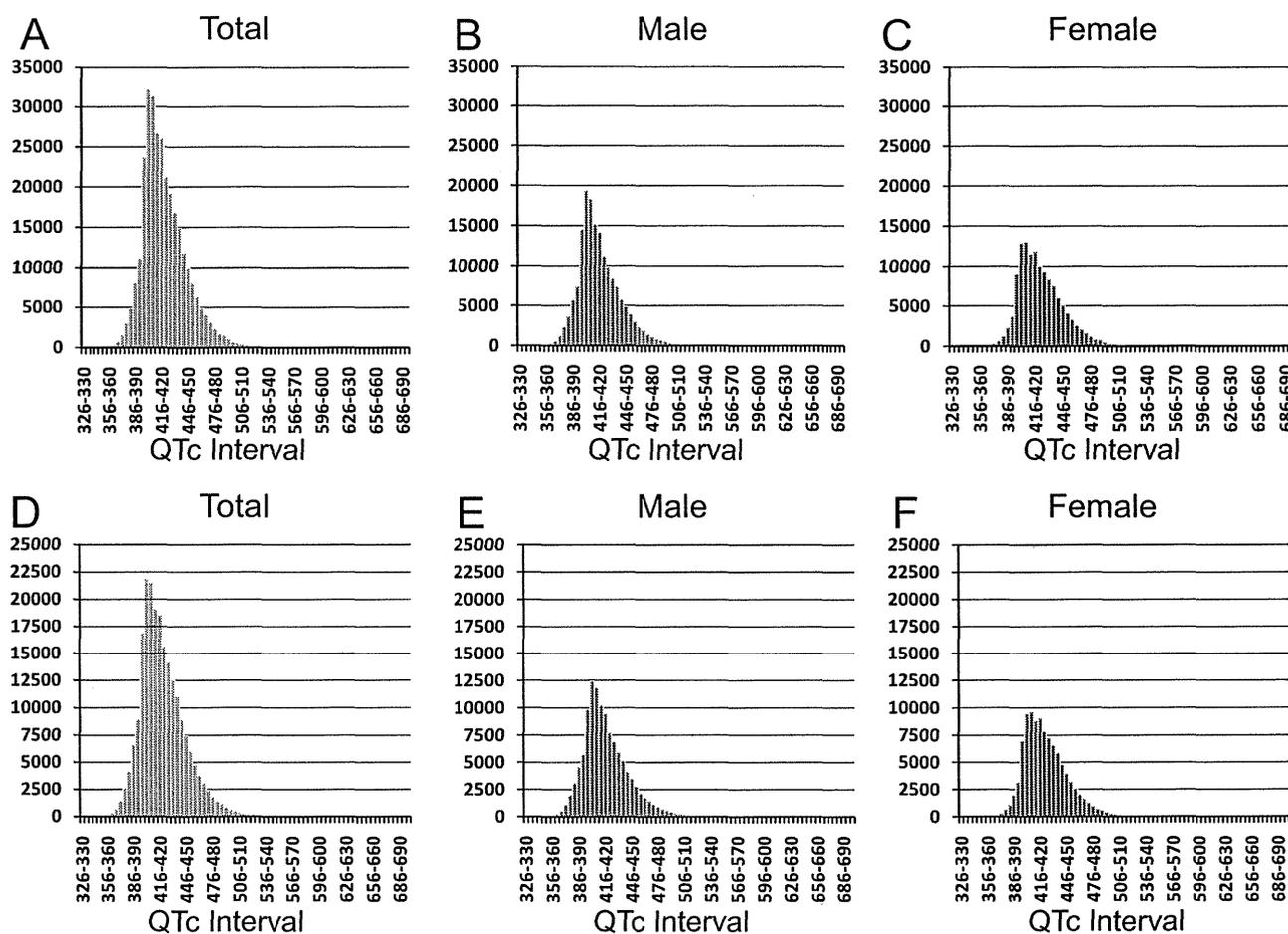
Figure 1   Distribution of Bazett QTc interval according to the number of patients (upper row) and the number of ECGs (lower row). Histograms of total, male, and female patients in this study population are displayed in panels A and D, B and E, and C and F, respectively.

in male patients. The QTc interval distributions did not fit a normal distribution curve (*P* <.01 for each) because the distributions were asymmetrical and right skewed. The histograms of QTc interval that were generated as a function of the number of patients are shown in the lower row of Figure 1. Similarly, the histograms of the QTc interval were right-skewed, which failed to fit to a normal distribution (*P* <.01 for each). The mode of QTc interval was 401 to 405 ms (range 329 to 693 ms), 401 to 405 ms (range 331 to 693 ms), and 406 to 410 ms (range 329 to 687 ms) in total, male, and female patients, respectively. Table 1 shows the lowest percentiles of QTc interval. The QTc interval at the lowest 2.5 percentile was longer than the lower limit of normal QTc interval previously reported.[9] The QTc interval[10,11] at the lowest 0.15 percentile was similar to the lower border of QTc interval. We therefore adopted a definition of short QT on the basis of previous studies, the cutoff value matching the 0.15 percentile of our whole population (234 male patients with QTc interval ≤362 ms, 193 female patients with QTc interval ≤369 ms). Furthermore, we divided the short QT population into percentiles and selected the 2.5 percentile of the short QT population as the very short QT (Table 2).

Clinical characteristics of short QT interval

Four hundred twenty-seven patients with short QT interval were chosen for the analysis according to the abovementioned rationale. The prevalence of patients with a short QT interval was about 1.2 times higher in male patients (N = 234) than in female patients (N = 193). The mean age was not different between male and female patients (41.9 ± 21.5 years vs 45.2 ± 23.4 years). Table 3 shows clinical characteristics of the patients with short and very short QTc intervals. The mean age was not different between short and

Table 1   The lowest percentiles of Bazett QTc interval for this study population

Percentile	Bazett QTc interval (ms)	
	Male	Female
2.5	380.0	387.0
2.0	378.0	386.0
1.0	373.0	381.0
0.5	369.0	376.0
0.15	362.0	369.0
0.1	361.0	367.0
0.0	331.0	329.0

Table 2 The percentiles for patients with short QT interval

Percentile	Bazett QTc interval (ms)	
	Male	Female
100	362.0	369.0
99.5	362.0	369.0
97.5	362.0	369.0
90	362.0	369.0
75	361.0	368.0
50	359.0	366.0
25	355.0	362.0
10	349.0	355.4
2.5	340.6	345.9
0.5	331.2	329.0
0.0	331.0	329.0

very short QT intervals in both genders. There was a 1.8-fold male predominance in patients with very short QT interval. There are various underlying diseases, in which rate did not differ between short and very short QTc intervals in both genders. Figure 2 shows the age-specific prevalence of total, male, and female patients with short QT interval. The histograms generated according to the number of patients are shown in the upper row of Figure 2. The prevalence was biphasic in each group, with a higher prevalence in young and old adults and with a lower prevalence in middle-aged individuals. The prevalence showed comparable distribution when histograms were generated according to a ratio of patients with short QT interval to total patients in each decade (the lower row in Figure 2).

ECG characteristics of short QT interval

Table 4 lists ECG characteristics. There was no significant difference in various ECG variables between patients with short and very short QT intervals. AF was present in 23 of 234 (9.8%) male and 16 of 193 (8.3%) female patients (P = NS). The prevalence of AF did not differ significantly be-

tween patients with short and very short QT intervals in both genders. The prevalence of early repolarization was significantly (P = .0001) higher in 23 of 234 (9.8%) male than in 3 of 193 (1.6%) female patients, but was not significantly different between patients with short and very short QT intervals in both genders. In these patients, 11 (42.3%) exhibited early repolarization in anterior leads (V1-4); 9 (34.6%) patients in inferolateral leads (II, III, aVF, V5, 6); and 5 (19.2%) patients in anteroinferior leads (V1-4, II, III, aVF).

Long-term outcome

Long-term prognosis was assessed in 327 of 427 (77%) patients (182 men; mean age, 46.4 ± 22.3 years) with short QT interval. The mean follow-up period was 54.0 ± 62.0 months (range 1.1 to 299.8 months). In patients whose prognosis was evaluated, QT interval was 360.3 ± 24.8 ms and QTc interval was 359.8 ± 7.1 ms. During the follow-up period, 2 male patients developed life-threatening events. One patient was a 22-year-old man who exhibited early repolarization. This patient was admitted to our hospital because he suffered from syncope when drinking in 1989. There was nephritic syndrome in his past medical history, but no family history of cardiac disorders or sudden unexplained death. On admission, 12-lead ECG exhibited early repolarization in ECG leads corresponding to the inferolateral wall of the left ventricle (Figure 3). This patient revealed no evidence of abnormality of cardiac function and morphology by transthoracic echocardiography. Coronary angiography failed to find morphological abnormality, and coronary spasm was not induced by ergonovine injection. However, ventricular fibrillation occurred when the ECG recording was taken after hyperventilation. Because sinus bradycardia preceded the occurrence of ventricular fibrillation, orciprenaline sulfate (30 mg/day) was administered. Seven years later, the patient experienced a storm of ven-

Table 3 Clinical characteristics in patients with short and very short QT intervals

	Male			Female		
	Very short (≤355 ms, N = 65)	Short (356 to 362 ms, N = 169)	P value	Very short (≤360 ms, N = 36)	Short (361 to 369 ms, N = 157)	P value
Age (yrs)	43.6 ± 23.4	41.2 ± 20.8	.46	46.3 ± 24.9	45.0 ± 23.1	.77
Hypertension (N, %)	13, 20.0	31, 23.9	.54	10, 27.8	27, 26.7	.90
Angina (N, %)	6, 9.2	15, 11.5	.62	1, 2.8	12, 11.9	.08
Myocardial infarction (N, %)	4, 6.2	3, 2.3	.19	2, 5.6	1, 1.0	.14
Valvular disease (N, %)	2, 3.1	8, 6.2	.34	3, 8.3	7, 6.9	.78
Heart failure (N, %)	12, 18.5	22, 16.9	.79	6, 16.7	18, 17.8	.88
Arrhythmia (N, %)	19, 29.2	25, 19.2	.12	7, 19.4	15, 14.9	.53
Diabetes (N, %)	8, 12.3	23, 17.7	.32	4, 11.1	15, 14.9	.57
Dyslipidemia (N, %)	7, 10.8	22, 16.9	.24	6, 16.7	18, 17.8	.88
Follow-up (months)	42.1 ± 47.3	54.0 ± 64.6	.20	49.3 ± 65.7	49.7 ± 62.7	.98
Death (N, %)	3, 4.6	3, 1.8	.24	0, 0	0, 0	—
Ventricular fibrillation (N, %)	1, 4.2	0, 0	—	0, 0	0, 0	—

Arrhythmia involves patients with various types of rhythm disorders, except for patients who exhibited AF when the ECG was taken. Surgery indicates patients who underwent ECG recording before surgical procedure. Others includes patients who suffered various internal diseases or who were suspected to have a cardiovascular disease.
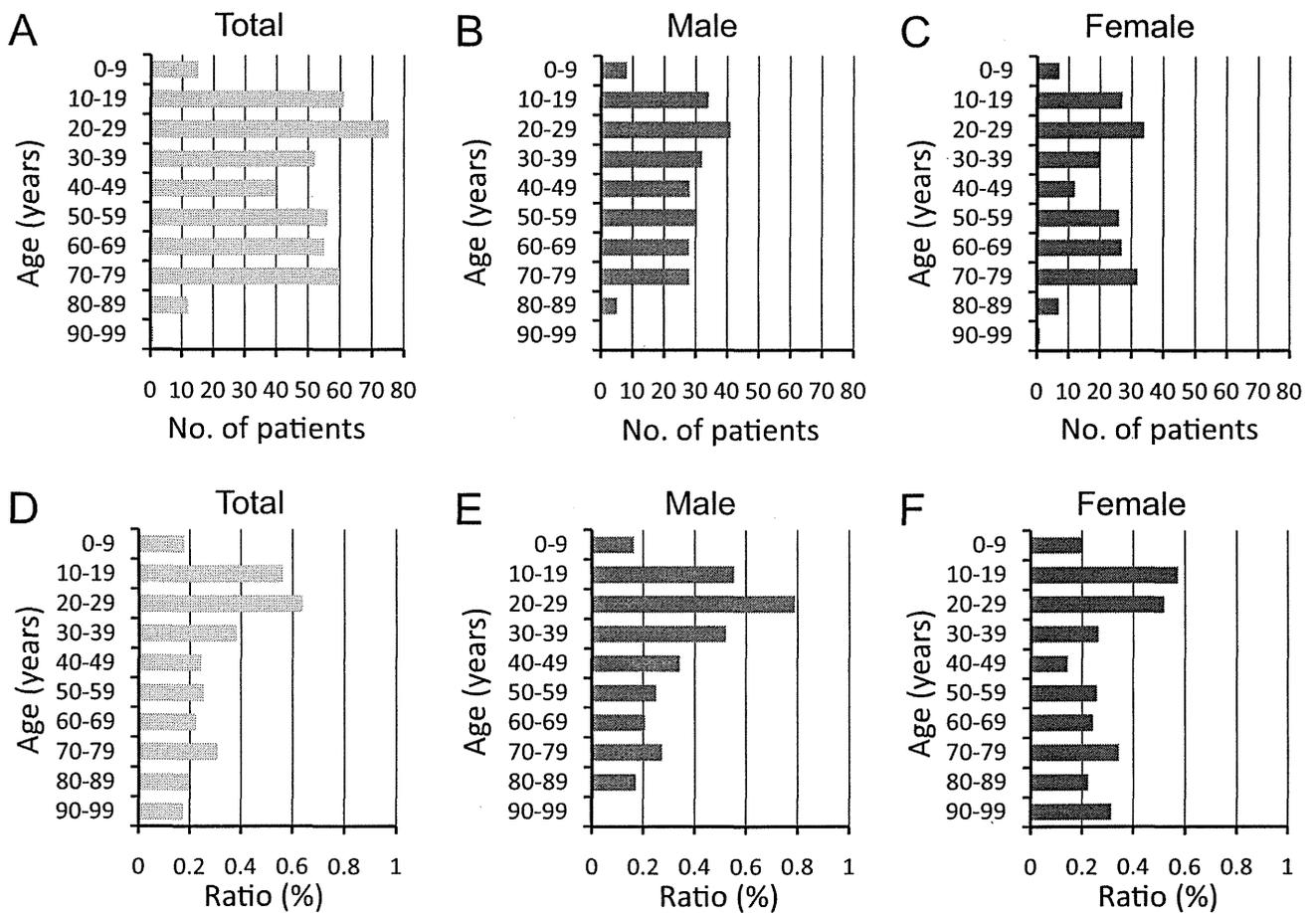
Figure 2 Age-specific prevalence of patients with short QT interval in decades according to the number of patients (upper row) and a ratio of patients to the total population of this study (lower row). Histograms of total, male, and female patients are displayed in panels A and D, B and E, and C and F, respectively.

tricular fibrillation (5 repetitive attacks per day) that occurred when bradycardia occurred (Figure 3B). A ventricular pacing lead was emergently introduced into the right ventricle to maintain rapid heart rate. Subsequently, a permanent pacemaker was implanted (DDDR mode, 80 beats/min). Six years after the storm, ventricular fibrillation recurred during a routine pacemaker check. Ventricular fibrillation repeatedly initiated after bradycardia because of

threshold margin check. The patient received an implantable cardioverter-defibrillator with atrioventricular sequential pacing applied at a rate of 85 beats/min. Another 54-year-old man developed repetitive syncopal episodes with urinary incontinence in 2001 when sleeping. This patient did not exhibit early repolarization (Figure 4). He did not have a family history of cardiac disorders or sudden unexplained death. This patient revealed no evidence of abnor-

Table 4 ECG characteristics in patients with short and very short QT intervals

	Male			Female		
	Very short (≤355 ms, N = 65)	Short (356 to 362 ms, N = 169)	P value	Very short (≤360 ms, N = 36)	Short (361 to 369 ms, N = 157)	P value
Heart rate (beats/min)	58.7 ± 8.3	60.3 ± 8.5	.20	60.6 ± 8.5	63.3 ± 9.8	.13
P wave axis (degree)	49.2 ± 37.5	47.8 ± 25.3	.77	47.7 ± 29.4	38.8 ± 28.5	.12
PQ interval (ms)	165.4 ± 37.2	163.4 ± 36.9	.75	161.7 ± 46.6	156.3 ± 39.0	.50
QRS complex duration (ms)	92.6 ± 8.4	92.3 ± 10.0	.82	87.5 ± 7.9	85.9 ± 8.4	.30
R wave axis (degree)	49.3 ± 32.8	57.3 ± 27.1	.060	50.6 ± 31.7	53.4 ± 26.4	.58
QT interval (ms)	357.4 ± 23.7	362.6 ± 22.9	.12	355.4 ± 25.0	360.2 ± 25.8	.31
T wave axis (degree)	46.8 ± 48.5	48.0 ± 34.9	.83	43.2 ± 45.4	48.0 ± 56.7	.64
Atrial fibrillation (N, %)	10, 15.4	13, 7.7	.089	1, 2.8	15, 9.6	.14
Early repolarization (N, %)	3, 4.6	20, 11.8	.076	1, 2.8	2, 1.3	.54
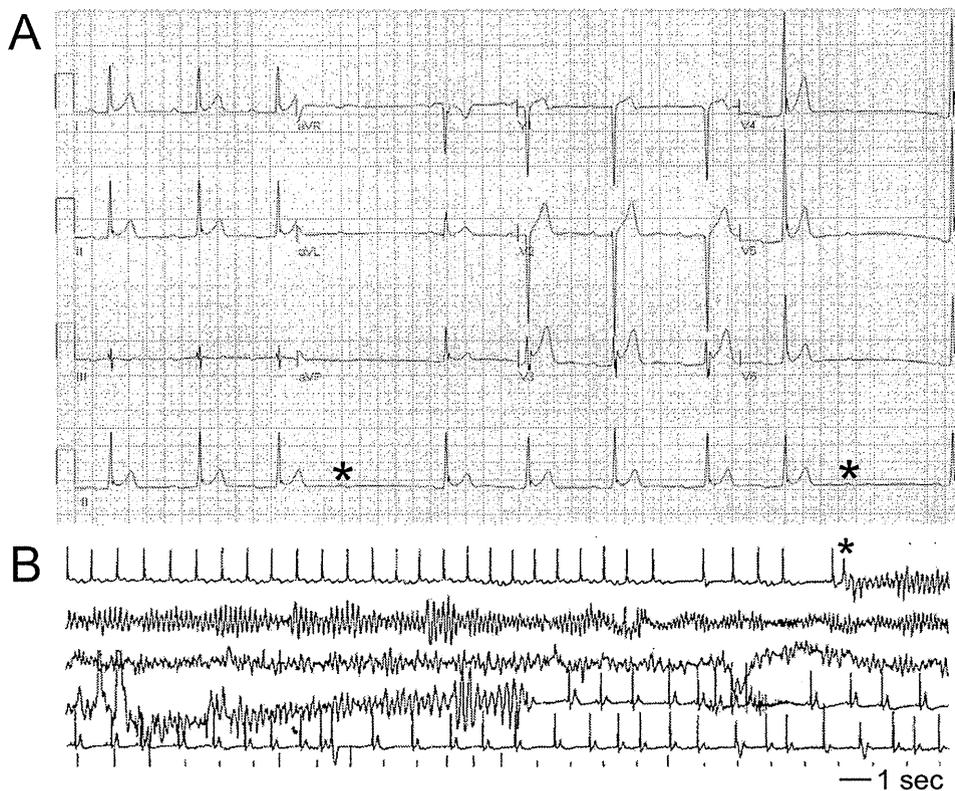
Figure 3   **A:** Twelve-lead ECG of a 22-year-old male patient who developed ventricular fibrillation. Mean heart rate is 50 beats/min; mean QT interval, 364 ms; and mean QTc interval, 332 ms. Early repolarization is present in leads I, II, aVF, and V3-6. *Nonconducting P wave due to Wenckebach atrioventricular block. **B:** Monitored ECG showing occurrence of ventricular fibrillation. *A short-coupled ventricular premature contraction initiated ventricular fibrillation that lasted for >1 minute and then self-terminated.

mality of cardiac function and morphology by transthoracic echocardiography and coronary angiography. His ECG showed Brugada-type ECG after intravenous administration of pilsicainide (Figure 4B). The ST-segment elevation in right precordial leads was accepted as sign of Brugada syndrome in the context of a clinical history, suggesting malignant syncope in this patient. To secure this patient from sudden death, an implantable cardioverter-defibrillator was implanted. These 2 patients did not have gene abnormalities, including *KCNQ1*, *KCNH2*, and *SCN5A*. In addition, we confirmed 6 deceased patients: 2 patients died of pneumonia at 70 and 72 years of age; 1 patient, congestive heart failure at 74 years of age; 1 patient, pancreatic cancer at 70 years of age; 1 patient, colon cancer at 74 years of age; and 1 patient, an unknown cause at 79 years of age. These 6 patients did not have early repolarization. AF was present in 1 patient who died of pneumonia.

Discussion

In the present study, we demonstrated detailed characteristics of patients with short[10-12] QT interval in a large hospital-based population. Consistent with previous reports, patients with short QT interval were rare and had a male preponderance. The age-specific prevalence of patients with short QT interval showed a biphasic distribution with a relatively low prevalence in middle-aged patients. Long-

term prognostic assessment revealed that 2 male patients with short QT interval suffered from life-threatening events in this study population.

Characteristics of short QT interval

The present study disclosed distinct characteristics regarding patients with short QT interval. The gender difference in the prevalence of short QT interval that was manifested in this study is presumably due to sex-specific biology, including hormone, membrane ion channel availability, and intracellular signal transduction. A male predominance of patients with short QT interval shown in this study is similar to the fact that QT interval is generally longer in female[13-15] than in male patients. Of interest, the pattern of prevalence of patients with short QT interval exhibited inhomogeneous distribution with 2 peaks at young and old ages in both genders. Although we do not know the mechanism by which this age-dependent distribution had 2 peculiar peaks in patients with short QT interval, one can speculate that the underlying mechanism of short QT interval may be different between young and aged patients because health condition is apparently diverse between them. Further investigations will be needed to explore the mechanism underlying the gender difference and age-specific distribution. Contrary to a previous report,[11] the prevalence of short QT interval in patients with heart rate of <50 beats/min (male, 2.4%;
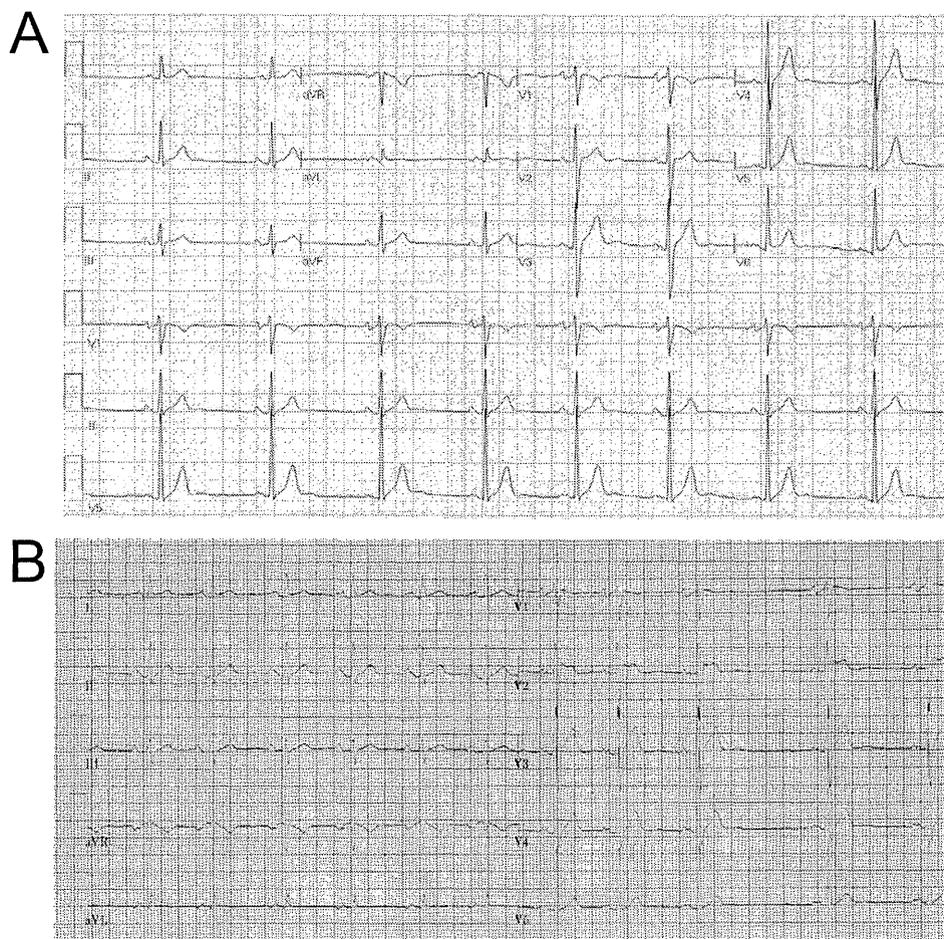
Figure 4   A: Twelve-lead ECG of a 54-year-old male patient who developed syncope repeatedly. Mean heart rate is 51 beats/min; mean QT interval, 386 ms; and mean QTc interval, 355 ms. Early repolarization is absent. **B:** ST-segment elevation in right precordial leads by intravenous administration of pilsicainide.

female, 1.6%) was comparable to that in total patients in this study. This is probably due to differential study populations; specifically, the present study population includes only hospital-based patients, and it is therefore possible that many of the patients with slow heart rate were receiving medications that prolonged their QT interval. In contrast, Kobza et al[11] reported on healthy army recruits. We investigated 2 ECG complications of short QT interval: AF and early[4,5,16,17] repolarization. It was reported that AF occurred in patients with short QT syndrome. In this study, the complication rate of AF was much higher compared with the prevalence of AF in the general population of Japan[18] and in total patients in this study (male, 4.1%; female, 1.9%), suggesting atrial involvement of abbreviated action potential with sharing the same mechanism as is present in the ventricle. Early repolarization was usually present in 1% to 5%[19,20] of general populations, which was regarded as benign. The prevalence of early[19,20] repolarization of this study was a little higher than that of those studies and that of the total population of this study (3.9%), but was lower than that of short QT syndrome.[8] To date, Haissaguerre et al[21] reported malignant early repolarization syndrome. In addition, Kamakura et

al[22] found that early repolarization was associated with poor outcome in patients with Brugada-type ECG. In these reports, early repolarization was present in inferolateral leads. In contrast, our patient had early repolarization most frequently in anterior leads. Thus, the location of early repolarization may matter in terms of occurrence of life-threatening events.

Short QT interval and short QT syndrome

There may be overlap between the QTc intervals of patients with and without inherited short QT syndrome.[9] The syndrome characterized by extremely abbreviated QT[23,24] interval causes sudden cardiac death. Gene mutation that causes a gain of function in the K^+ channel is attributed to this shortening in this syndrome, suggesting that a specific family[5,16,25] member is affected with this disorder. In general, the QTc interval was <300 ms[4,5,26,27] in subjects with short QT syndrome. In contrast, Antzelevitch et al reported Brugada-type ST-segment elevation in probands whose QT interval was approximately 360 ms. In their cases, gene mutation encoding L-type calcium channel was detected, and those subjects died suddenly. Recently, a mutation of

KCNJ8 was identified in patients with idiopathic ventricular fibrillation and early repolarization, which might be attributed to sudden death.[28] A new mutation in calcium channel regarding congenital short QT syndrome type 6 was reported.[29] A proband of this mutation had a short QT interval of 329 ms; however, a genotype-positive grandmother had a normal QT interval of 432 ms, although she had myocardial infarction. This study suggests that a phenotypical QT interval might be modified by myocardial necrosis in this syndrome, giving rise to normalization. Thus, one has to consider lack of genotype-phenotype correlation in short QT syndrome. However, genetic mutation was not detected in 2 patients who experienced life-threatening events in this study. Therefore, further investigations of gene analysis are needed in these patients.

Arrhythmogenesis in short QT interval

Gallagher et al[12] reported that a QTc interval of ≤330 ms was extremely rare in healthy subjects and did not bear a significant risk of sudden death. However, in our hospital-based population, 2 patients with short QTc interval developed life-threatening events. An experimental study that dealt with an association of early repolarization with ventricular fibrillation showed that modulating factors amplified transmural electrical heterogeneity that caused early repolarization to generate reentry.[26] In this study, 1 patient who experienced bradycardia-dependent occurrence of ventricular fibrillation presented J wave. This finding suggests manifestation of transmural electrical gradient during slow heart rate,[30–32] which is consistent with previous reports. Another patient who exhibited Brugada-type ECG after the administration of sodium channel blocker suggests that a mechanism underlying life-threatening events in short QT syndrome may be similar to a mechanism accounting for ventricular fibrillation in Brugada syndrome. In clinical practice, it is difficult to diagnose short QT syndrome unless a subject is symptomatic. Indeed, 2 patients who had developed life-threatening events in this study were found to have a short QT interval afterward. This finding indicates incidental discovery of short QT syndrome.

Study limitations

First, patients enrolled in this study were derived from a hospital-based population, indicating that our data do not properly apply to a general population. Because our data were based on the hospital population, patients who had organic heart diseases or took drugs with QT-prolonging effects were involved. We could not search medication uses thoroughly, as Ramirez et al[33] did. In addition, patients with bundle branch block or pre-excitation syndrome were not excluded from the analysis. The QT interval was longer when computer-assisted measure was performed as compared with manual measure of QT interval in lead V5. These underlie the right-skewed distributions of QTc interval. The fact that we included patients with medications probably had a limited effect on the number of patients with very short QT because medications (and conditions such as bun-

dle branch block) tend to prolong the QT, not to shorten it. Second, we could assess the prognosis of 327 patients (77%) with short QT interval. However, the long-term outcome was not thoroughly investigated and the follow-up period was not long enough. Further assessment is necessary to clarify the prognosis of patients with short QT interval. Third, it must be considered how to correct QT interval. Correlation of QT interval by the Bazett formula has a tendency to overestimate or underestimate QT interval when heart rate is particularly fast or slow, respectively. We first set the heart rate to ranging from 50 to 100 beats/min not to include overestimation and underestimation of QT interval by the Bazett formula. Even in an additional analysis in patients with heart rate <50 beats/min, the prevalence of short QT interval was similar to that in the first analysis. This might be attributed to our hospital-based population.

Conclusion

Until now, there have been mounting reports of short QT syndrome. Nevertheless, ECG features of prognostic significance are still lacking. This study proposed that early repolarization concomitant with short QT interval indicates a potential for sudden cardiac death. The complication rate of AF and early repolarization was higher in patients with short QT interval than in a general population and total patients of this study. Although our database contains a huge number of ECGs, we could assess a rather small group of patients with short QT interval. This implies that multicenter clinical research will be required to further determine the prognostic value of short QT interval. Despite the small number of patients enrolled in this study, the findings could shed light on the prognostic value of early repolarization in patients with short QT interval.

Acknowledgements

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.08.016.

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