c.C2212T in a heterozygous manner (Fig. 2) causing a stop codon at 738 (p.Q738X). No other mutations were found in LQTS-associated genes such as KCNQ1, KCNE1, KCNE2, KCNJ2 and SCN5A. By informing of the risk of sudden death, she underwent implantation of dual chamber ICD. After the implantation, she has experienced no syncope

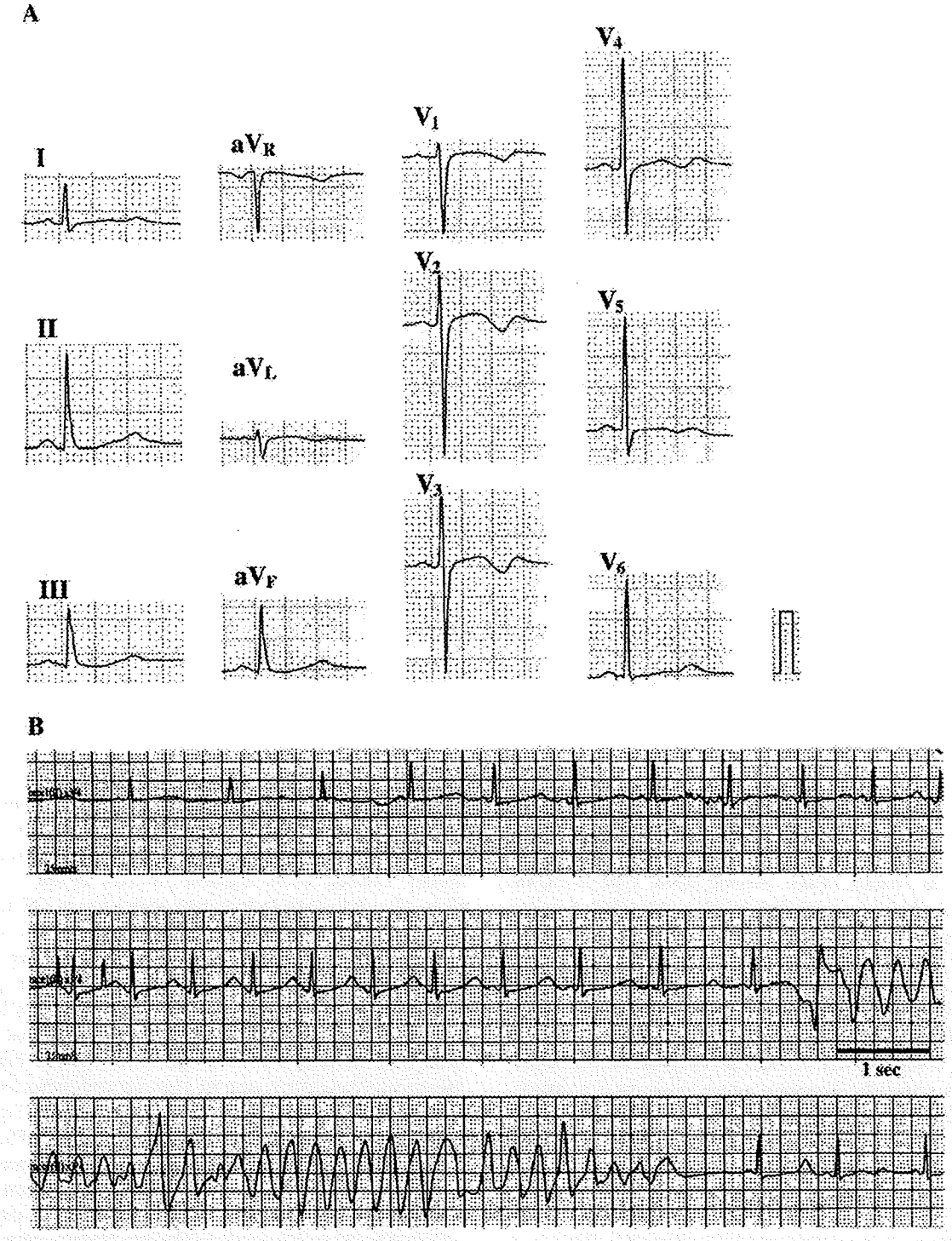

Fig. 1. A; Standard ECG of proband showed QT interval of 520 ms and flat T wave. B; Ambulatory monitoring demonstrated lack of rate adaptation in QT interval and subsequent Torsades de Pointes in the morning. C; Her father showed atrial flutter with ventricular pacing. D; Her daughter exhibited long QT (480 ms) with broad-based, sharp T wave.

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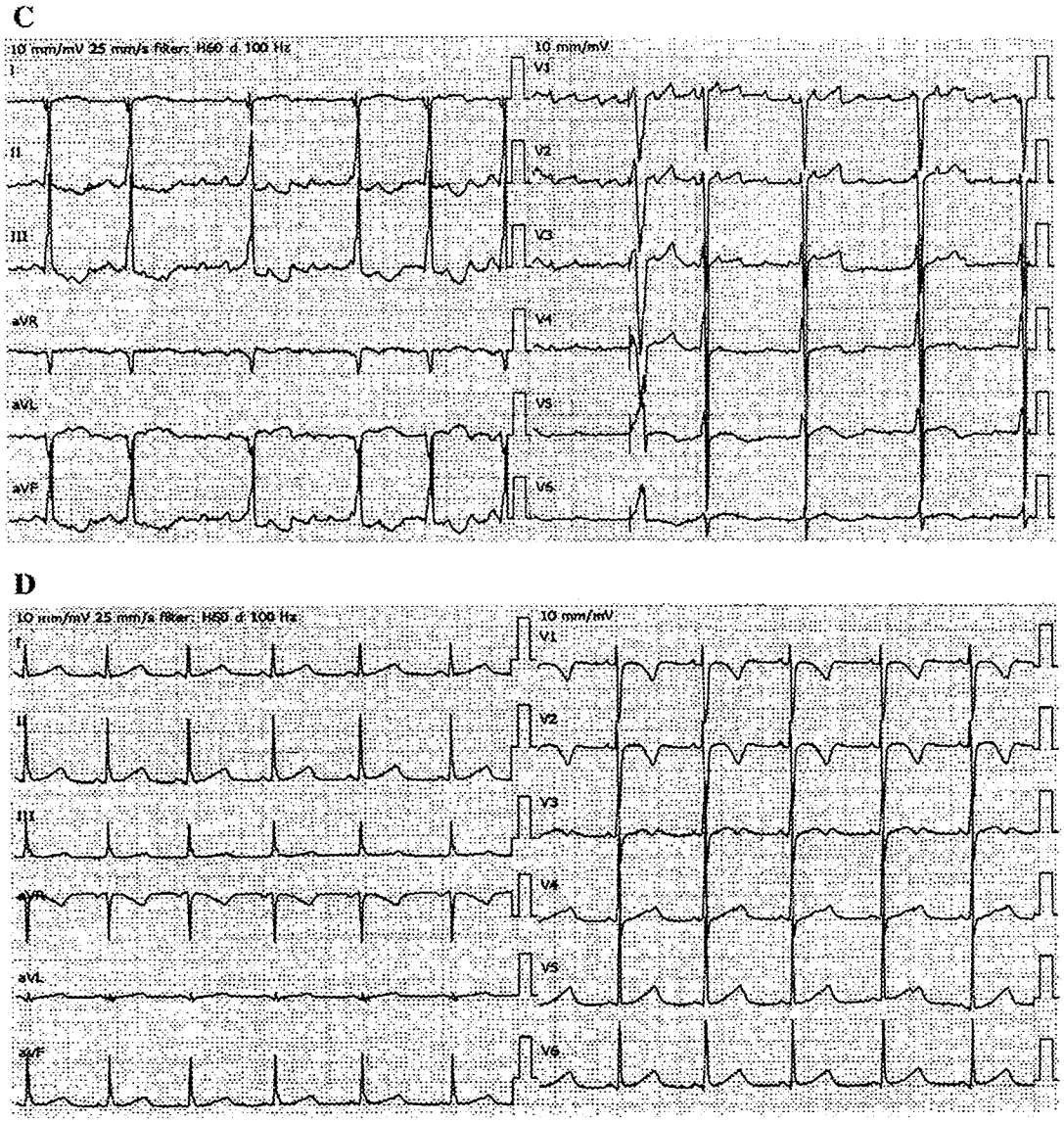

Fig. 1 (*continued*).

without ICD discharge. Her daughter is asymptomatic under careful observation without device or medication.

It is of great interest that ECG phenotypes in this LQT2 family showed a considerable variation, i.e., the proband showed ECG compatible to LQT2 (Fig. 1A) and no rate adaptation of QT interval, postexercise QT prolongation and subsequent TdP (Fig. 1B), which is observed in 13% of overall cardiac events in LQT2 patients [2], whereas her father had advanced AV block and subsequent persistent atrial flutter with normal QT interval (Fig. 1C), and her daughter showed long QT interval with broad-based, tall T wave (Fig. 1D). Reportedly, various kinds of atrial tachyarrhythmias are associated with LQTS [4]. T wave morphology recorded in her daughter is observed mainly in LQT1 but in 32% of LQT2 [3].

HERG K channel conducts rapid component of delayed rectifier K current (I_{Kr}), which is essential for normal cardiac repolarization. To our knowledge, Q738X HERG mutation has not been registered in HERG-related Online Mendelian Inheritance in Man (OMIM; http://pc4.fsm.it:81/cardmoc). The Q738X product results in the deletion of 86% of the C-terminus. Since a single HERG channel protein consists of four α-subunits, the truncated subunit based on Q738X would hinder the normal assembly of healthy subunits and therefore exerting a dominant negative suppression effects. Although an *in vitro* expression study was not performed, these effects are considered to suppress I_{Kr} profoundly and yield the LQT2 phenotypes in the proband and her family. However, the nonsense Q738X mutation may cause a nonsense-mediated mRNA decay

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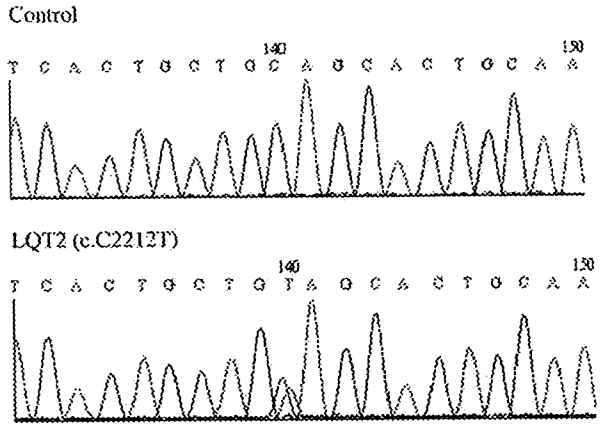

Fig. 2. Mutation analysis of family members. Chromatograms showed a common single nucleotide mutation of c.C2212T, causing amino acid sequence of p.Q738X.

(NMD) and avoid dominant negative suppressions as a post-transcriptional control. The severity of the phenotypes would therefore differ depending on the degree of NMD level [5]. This may be a main reason for varied QT intervals and T wave morphologies in this relatively small LQT2 family.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

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Please cite this article as: Yasuda S, et al. A family of hereditary long QT syndrome caused by Q738X HERG mutation. Int J Cardiol (2009), doi:10.1016/j.ijcard.2008.12.053

High prevalence of early repolarization in short QT syndrome

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BACKGROUND Short QT syndrome (SQTS) is characterized by an abnormally short QT interval and sudden death. Due to the limited number of cases, the characteristics of SQTS are not well understood. It has been reported recently that early repolarization is associated with idiopathic ventricular fibrillation and the QT interval is short in patients with early repolarization.

OBJECTIVE The purpose of this study was to study the association between early repolarization and arrhythmic events in SQTS.

METHODS The study consisted of three cohorts: SQTS cohort (N = 37), control cohort with short QT interval and no arrhythmic events (N = 44), and control cohort with normal QT interval (N = 185). ECG parameters were compared among the study cohorts.

RESULTS Heart rate, PR interval, and QRS duration were similar among the three study cohorts. Early repolarization was more common in the SQTS cohort (65%) than in the short QT control cohort (30%) and the normal QT control cohort (10%). Duration from T-wave peak to T-wave end was longer in the SQTS cohort than in the short QT control cohort, although QT and corrected QT intervals were similar. In the SQTS cohort, there were more males among patients with arrhythmic events than in those with a family history but without arrhythmic events. In multivariate models, early repolarization was associated with arrhythmic events in the SQTS cohort. ECG parameters including QT and QTc intervals were not associated with arrhythmic events in the SQTS cohort.

CONCLUSION There is a high prevalence of early repolarization in patients with SQTS. Early repolarization may be useful in identifying risk of cardiac events in SQTS.

KEYWORDS Arrhythmia; Electrocardiogram; QT interval; Repolarization; Sudden death

ABBREVIATIONS **QTc** = corrected QT interval; **SQTS** = short QT syndrome

Introduction

The short QT syndrome (SQTS) is characterized by an abnormally short QT interval and increased risk of ventricular fibrillation and sudden death.[1,2] Similar to other arrhythmia syndromes, such as long QT syndrome and Brugada syndrome,[3] SQTS is a genetically heterogeneous disease, and, to date, five responsible genes encoding different ion channels have been identified.[3–7] Some inherited arrhythmia syndromes may share genetic backgrounds that result in overlapping arrhythmia phenotypes.[3]

Although early repolarization is generally considered benign,[8] it has been reported recently that early repolarization is associated with increased risk for sudden cardiac death in patients with idiopathic ventricular fibrillation.[9–12] Haissaguerre et al[9] reported that, among patients with idiopathic ventricular fibrillation, the QT interval was shorter in patients with early repolarization than in those without, suggesting an association between early repolarization and QT interval shortening. Evidence that mutations in calcium channel genes are associated with Brugada-type ST-segment elevation and abnormally short QT intervals further suggests a relationship between early phase repolarization abnormalities and short QT interval.[4] Here we report on our

Drs. T. Makiyama, M. Horie, and W. Shimizu were supported in part by the Research Grant for the Cardiovascular Diseases (21C-8) from the Ministry of Health, Labour and Welfare, Japan. **Address reprint requests and correspondence:** Dr. Wataru Shimizu, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail address: wshimizu@hsp.ncvc.go.jp. (Received November 29, 2009; accepted January 9, 2010.)

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2010.01.012

study of the prevalence of early repolarization and its association with arrhythmic events in SQTS.

Methods

This cooperative study consisted of three cohorts. (1) *SQTS cohort* included patients with SQTS referred to our institutions and patients with SQTS from previous reports. The diagnosis of SQTS was made if a patient with a short QT interval [corrected QT interval (QTc) by Bazett formula ≤330 ms] had an arrhythmic event including documented ventricular fibrillation, resuscitated sudden cardiac death, and syncope and/or had a family history of SQTS, or if a patient with a short QT interval (QTc ≤360 ms) had mutations in ion channel genes responsible for SQTS.[3,13] We searched in the electronic databases PubMed, EMBASE, and Cochrane for all published studies that examined patients with SQTS. The search was limited to the end of June 2009. Published studies were considered eligible if they included clinical characteristics of the patients and ECGs. All ECGs from patients reported in the literature were reanalyzed. Electrophysiologic study was performed in patients with SQTS based on the indication of each institution. (2) *Control cohort with short QT interval* (QTc ≤330 ms) *and no arrhythmic events* was selected from among 86,068 consecutive ECGs stored on the ECG database at Niigata University Medical and Dental Hospital from May 7, 2003 to July 2, 2009. Subjects who did not have arrhythmic events or cardiovascular disease and were not taking any medication were included in this cohort. (3) *Control cohort with normal QT interval* was also selected from the ECG database. This cohort consisted of subjects who were matched to the SQTS cohort for gender and age. Subjects who had normal QT interval (360–440 ms) and did not have cardiovascular disease or were not taking any medication were included in this cohort. Subjects with Brugada-type ST-segment elevation were excluded from all study cohorts.[3,9]

QT intervals were measured on lead V_2 with the tangent methods for determination of QT_{end} using a semi-automated digitizing program with electronic calipers by an experienced observer blinded to the clinical details of all subjects included in this study.[14,15] Early repolarization was defined as elevation of the J point noted as either as QRS slurring or notching ≥0.1 mV in more than two leads.[9]

Differences in parameters were analyzed using multivariable logistic regression models when SQTS cohort and control cohort with short QT interval were compared and analyzed using conditional logistic regression models when SQTS cohort and control cohort with normal QT interval were compared. All statistical analyses were performed with SPSS (version 12.0, SPSS, Inc., Chicago, IL, USA). Two-sided $P < .05$ was considered significant. Values are expressed as mean ± SD. The study protocol was approved by the Ethics Committee of Niigata University School of Medicine. To determine interobserver variability, a second observer made independent blinded QT interval determinations of all study subjects with short QT interval.

Results

Thirty-seven patients with SQTS were identified: 12 from our institutions and 25 reported in the literature,[2,5,6,14,16–25] Forty-four control subjects with short QT interval and 185 control subjects with normal QT interval also were identified (Table 1). The SQTS cohort consisted of 25 (68%) patients with symptoms, including 14 with cardiac arrest (3 sudden death, 11 resuscitated) and 11 with syncope. Genetic screening identified mutations in ion channels in 7 (41%) of 17 probands who were genetically screened (2 *KCNQ1*, 4 *KCNH2*, 1 *KCNJ2*). Among patients in our institutions and those reported in the literature, there was no difference with regard to gender, age, prevalence of family history, QT or QTc interval, or inducibility of ventricular tachyarrhythmia by electrical programmed stimulation.

Heart rate, PR interval, and QRS duration in the SQTS cohort were not different among patients in either the short QT control cohort or the normal QT control cohort (Table 1). QT and corrected QT intervals were shorter in the SQTS and short QT control cohorts than in the normal QT control cohort. Early repolarization occurred in 24 (65%) patients with SQTS (Figure 1). Interobserver variability between two investigators was 8.6 ms (95% confidence interval −0.5 to 17.7 ms) for QT interval and 9.0

Table 1 ECG parameters of study cohorts

	Patients with SQTS (N = 37)	Subjects with short QTc (N = 44)	Versus subjects with short QTc*		Subjects with normal QTc† (N = 185)	Versus subjects with normal QTc	
			OR (95% CI)	*P* value		OR (95% CI)	*P* value
Male gender [N (%)]	27 (73)	34 (77)	2.84 (0.72–11.2)	.14	135 (73)	—	—
Age (years)	30 ± 19	47 ± 23	1.05 (1.02–1.08)	.001	30 ± 19	—	—
Heart rate (bpm)	69 ± 393	65 ± 398	1.00 (1.00–1.01)	.3	70 ± 327	1.00 (1.00–1.00)	0.70
PR interval (ms)	138 ± 19	153 ± 38	1.01 (0.99–1.03)	.54	143 ± 24	0.99 (0.97–1.01)	0.18
QRS interval (ms)	86 ± 7	84 ± 8	0.97 (0.91–1.04)	.38	85 ± 7	1.01 (0.96–1.06)	0.74
QT interval (ms)	286 ± 36	286 ± 15	0.99 (0.97–1.01)	.28	367 ± 36	0.97 (0.96–0.98)	<0.001
QTc (ms)	308 ± 29	299 ± 21	0.98 (0.96–1.00)	.06	399 ± 24	0.97 (0.97–0.98)	<0.001

CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.
*Models were adjusted for gender and age.
†Gender and age were matched between patients with SQTS and subjects with normal QT interval.

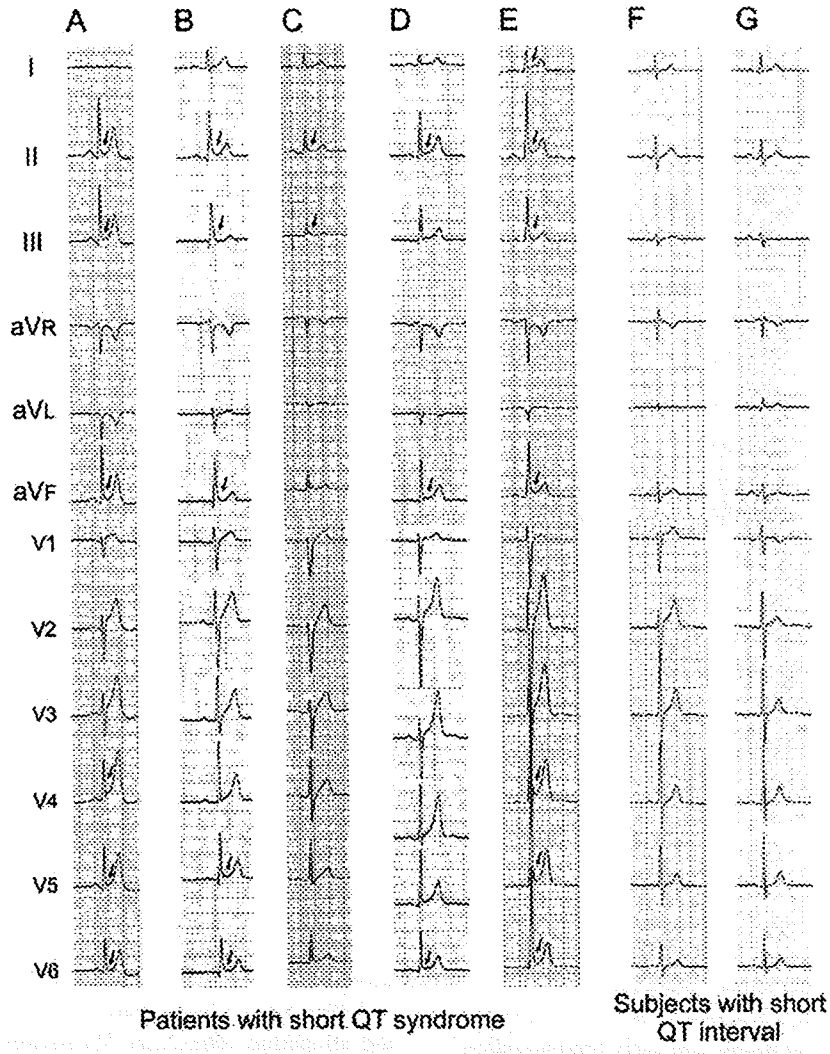

Figure 1 Early repolarization in short QT syndrome. ECGs were recorded from patients with short QT syndrome (**A:** 61-year-old woman; **B:** 30-year-old man; **C:** 38-year-old man; **D:** 31-year-old man; **E:** 22-year-old man) and control subjects with a short QT interval (**F:** 23-year-old man; **G:** 44-year-old woman). In each patient with short QT syndrome, early repolarization was evident in the inferolateral leads (*arrows*).

ms (95% confidence interval −0.6 to 18.7 ms) for QTc interval. The frequency of early repolarization was not different between patients in our institutions and those reported in the literature. Early repolarization was present in the inferior leads (II, III, aVF) in 9 patients, in the lateral leads (I, aVL, V_4–V_6) in 6 patients, and in both the inferior and lateral leads in 9 patients. Of 10 probands with early repolarization genetically screened, mutations were identified in 3 patients (1 *KCNQ1*, 2 *KCNH2*). Early repolarization was more common in the SQTS cohort than in the short QT control and normal QT control cohorts (Figure 2).

The association of early repolarization with arrhythmic events then was studied in patients with SQTS. In the SQTS cohort, there were more males among patients with arrhythmic events than among those with a family history but without arrhythmic events (Table 2). In multivariate models adjusted for gender and age, early repolarization was associated with arrhythmic events, although ECG parameters including QT and QTc intervals were not associated with arrhythmic events. Early repolarization remained associated with arrhythmic events after adjustment for age, gender, and QTc interval (P = .001). Electrophysiologic study performed in 18 patients with SQTS revealed no difference in inducibility of ventricular tachyarrhythmia between patients with arrhythmic events (73%) and those without arrhythmic events (71%).

QT interval parameters were compared between SQTS and short QT control cohorts because some of the parameters recently have been associated with SQTS.[26] Interval from T-wave peak to T-wave end (T_{peak} to T_{end}) was longer in the SQTS cohort than in the short QT control cohort even after heart rate correction using the Bazett formula, whereas QT interval, QTc interval, and interval from Q-wave to T-wave peak (QT_{peak}) were not different between the two cohorts (Table 3). Ratio of T_{peak} to T_{end} per QT was larger in the SQTS cohort than in the short QT control cohort.

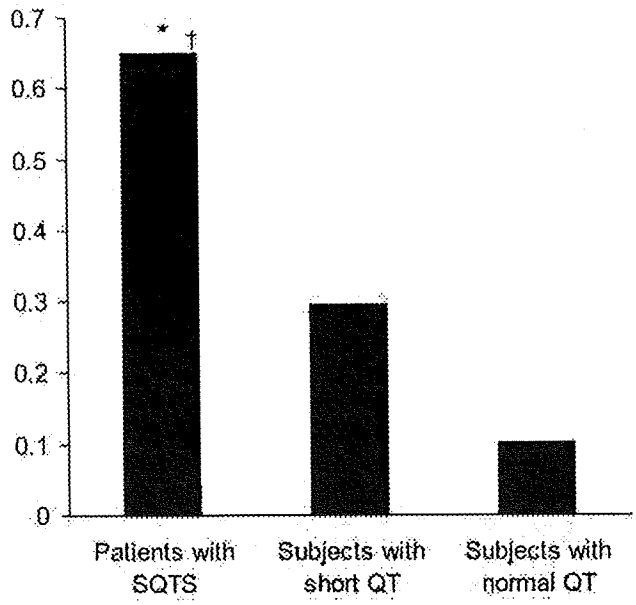

Figure 2 Frequency of early repolarization. Odds ratios (95% confidence intervals) for early repolarization in patients with short QT syndrome (SQTS) were 5.64 (1.97–16.15) and 16.58 (7.2–38.21) versus subjects with short QT interval and those with normal QT interval, respectively. *P = .001 vs subjects with short QT interval. †P <.001 vs subjects with normal QT interval.

Discussion

SQTS is a recently discovered, very rare disease with an increased risk of sudden death.[2] Due to the limited number of cases, the characteristics of SQTS are not well understood. Therefore, we conducted a cooperative analysis of ECGs from patients with SQTS in our institutions and those reported in the literature and found that early repolarization is common in SQTS.

Early repolarization is a common ECG finding. It is present in 1% to 13% of the general population and usually is considered as a normal variant due to its benign long-term prognosis.[8,11,27–29] However, increasing evidence suggests that early repolarization is associated with arrhythmia.[9,27,30–34] Since 1985, we and other investigators have reported an association between early repolarization (or late depolarization) and sudden cardiac death.[30–32] A multicenter study including our institution recently showed that early repolarization is present in one third of patients with idiopathic ventricular fibrillation.[9] Early repolarization is associated with increased risk of sudden cardiac arrest in idiopathic ventricular fibrillation, and the amplitude of early repolarization increases before development of arrhythmic events.[9,10] In Brugada syndrome, which is characterized by J-wave and ST-segment elevation in the right precordial leads on ECG and sudden cardiac death,[3] early repolarization in the inferolateral leads is not uncommon and is associated with arrhythmic events,[34] although another report has shown negative results.[33] In our study, early repolarization in the inferolateral leads was frequently found in SQTS and, more importantly, was associated with arrhythmic events in SQTS. In addition to arrhythmia syndromes unassociated with structural heart disease, a high frequency of early repolarization in arrhythmogenic right ventricular dysplasia/cardiomyopathy has been reported.[27]

It has been suggested that SQTS and idiopathic ventricular fibrillation share clinical characteristics.[23] Short QT interval is frequently found in idiopathic ventricular fibrillation,[23] and QT interval is relatively short in patients with idiopathic ventricular fibrillation who have early repolarization.[9] Spontaneous and inducible ventricular fibrillation can be initiated by short-coupled premature ventricular beat in SQTS and idiopathic ventricular fibrillation.[21,35,36] The efficacy of isoproterenol and quinidine has been reported for both arrhythmia syndromes,[21,37] although the arrhythmogenic effects of isoproterenol in an experimental model of SQTS have been reported.[38] Our study showing an association of early repolarization with SQTS further supports the presence of common arrhythmogenic substrates in SQTS and idiopathic ventricular fibrillation.

A precise mechanism for ventricular fibrillation in SQTS is not known, but characteristic ECG abnormalities may reflect arrhythmogenicity. A prior study showed that the interval from T-wave peak to T-wave end is relatively long in SQTS, and our study replicated the results.[26] T-wave peak to T-wave end interval is considered to reflect transmural dispersion of repolarization, and relative prolongation of the interval in SQTS may indicate a high vulnerability to ventricular fibrillation.[39] An experimental model of SQTS

Table 2 Characteristics of SQTS patients with and those without arrhythmic events

	Patients with arrhythmic events (N = 25)	Patients without arrhythmic events (N = 12)	OR (95% CI)	*P* value
Male gender [N (%)]	21 (84)	6 (50)	10.44 (0.85–127.48)	.07
Age (years)	30 ± 19	23 ± 18	1.05 (0.99–1.12)	.13
Heart rate (bpm)	69 ± 393	76 ± 473	1.00 (1.00–1.01)	.38
PR interval (ms)	138 ± 19	134 ± 18	0.99 (0.95–1.04)	.84
QRS interval (ms)	86 ± 7	85 ± 10	0.93 (0.82–1.07)	.31
QT interval (ms)	286 ± 36	271 ± 40	1.00 (0.97–1.03)	.75
QTc (ms)	308 ± 29	306 ± 33	0.98 (0.94–1.02)	.33
Early repolarization [N (%)]	22 (88)	2 (17)	46.53 (4.52–478.79)	.001

CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.
Models were adjusted for gender and age.

Table 3 ECG parameters for study cohorts with short QT interval

	Patients with SQTS	Subjects with short QTc	OR (95% CI)	*P* value
QT_{peak} (ms)	211 ± 37	222 ± 19	0.99 (0.98–1.01)	.37
Corrected QT_{peak}	226 ± 32	234 ± 24	0.99 (0.98–1.01)	.56
T_{peak} to T_{end} (ms)	81 ± 21	67 ± 13	1.08 (1.03–1.13)	<.001
Corrected T_{peak} to T_{end}	89 ± 28	72 ± 17	1.05 (1.02–1.09)	.002
QT_{peak}/QT ratio (%)	27 ± 6	22 ± 4	0.83 (0.73–0.94)	.004

Models were adjusted for gender and age.
CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.

provides evidence that increased transmural dispersion of repolarization under short QT interval conditions results in ventricular tachyarrhythmia.[38] A tall peaked T wave is one of the characteristic ECG abnormalities in SQTS,[1] but the amplitude of the T wave is not different between patients with SQTS and subjects with short QT interval and no arrhythmic events, suggesting that a tall T wave is associated with a short QT interval but is not associated with arrhythmogenicity.[26] In SQTS, characteristic ECG abnormities are also found in the early repolarization phase. In patients with SQTS, the ECG shows a very short J-point to T-wave peak interval and no flat ST segment.[26] In our study, early repolarization was frequently found in SQTS and was associated with arrhythmic events. Whether the inferolateral J-point elevation reflects late depolarization or early repolarization is controversial, but this pattern has been considered repolarization because of slower inscription, spontaneous changes occurring concurrently with ST segment but not with QRS complexes, and absence of late potentials on signal-averaged ECG.[9,40] Taken together, the finding suggest that abnormalities in the early phase of repolarization create the arrhythmogenic substrate in SQTS.

Sex hormone and gender difference have an important role in the arrhythmia syndromes.[41–43] It is well known that the QT interval is affected by sex hormones, and the QT interval is longer in women than men.[44] Female gender is a risk factor for development of ventricular tachyarrhythmias in both congenital and acquired long QT syndrome.[41,42] On the other hand, Brugada syndrome is more prevalent in men than in women, and the male hormone testosterone is reported to contribute to male predominance in Brugada syndrome.[43] In this study, male gender was associated with arrhythmic events in SQTS and short QT interval was frequently found in men, suggesting a role of sex hormones in SQTS opposite to that in long QT syndrome. Recent evidence that the QT interval can be shortened by anabolic androgenic steroids and testosterone further supports this hypothesis.[45,46]

SQTS is a genetically heterogeneous disease with five responsible genes encoding ion channels: *KCNQ1*, *KCNH2*, *KCNJ2*, *CACNA2D1*, and *CACNB2b*.[3,4] An increase in outward current by gain-of-function mutations in potassium channels or a decrease in inward current by loss of function mutations in calcium channels may be responsible for SQTS.[3,4] Early repolarization was found in patients with mutations in *KCNQ1* and *KCNH2* and in those without mutations in the known genes, suggesting a heterogeneous genetic background for the association between short QT interval and early repolarization. To date, mutations in calcium channel genes (*CACNA2D1* and *CACNB2b*) have been identified in three probands with Brugada syndrome associated with a short QT interval, but early repolarization is not present in the inferolateral leads in any of them.[4] A recent study has identified a mutation in *KCNJ8*, an initial responsible gene for idiopathic ventricular fibrillation associated with early repolarization.[47] Although there are some similarities in phenotype between SQTS and idiopathic ventricular fibrillation with early repolarization, a common genetic background has not been identified.

Conclusion

Our study showed a high prevalence of early repolarization in patients with SQTS and an association of early repolarization with arrhythmic events. Early repolarization may be a useful marker for risk stratification of cardiac arrest in SQTS, although further investigation with longitudinal follow-up is required to evaluate our results.

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IJCA-12005; No of Pages 4

International Journal of Cardiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Edior

A novel SCN5A mutation associated with the linker between III and IV domains of $Na_v1.5$ in a neonate with fatal long QT syndrome

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ARTICLE INFO

Article history:
Received 8 April 2009
Accepted 11 April 2009
Available online xxxx

Keywords:
Long QT syndrome
Fetal arrhythmia
SCN5A
Linker of III–IV domains

ABSTRACT

A male newborn weighing 2334 g was delivered at 37 weeks of gestation by caesarean section because of prenatal ultrasound findings of fetal hydrops with atrioventricualr block, ventriucular tachycardia (VT), and impaired ventricular function. In spite of the intravenous administration of lidocaine, VT continued. He developed poor perfusion and systemic hypotension. After the intravenous administration of amiodarone, VT was terminated. The electrocardiogram revealed an extremely prolonged corrected QT interval (860 ms) with 2:1 atrioventricular block. Unfortunately, he died 18 h after birth in spite of the administration of lidocaine, beta-blocker and magnesium. Mutational analysis identified a novel heterozygous *de novo* mutation (F1486del) in *SCN5A*. This mutation is associated with the IFM motif in the linker between III and IV domains of $Na_v1.5$, which serves as an inactivation particle binding within the pore of sodium channels. This report demonstrates an interesting relationship between the clinical phenotype and the location of the mutation in long QT syndrome.

1. Introduction

Congenital long QT syndrome (LQTS) is a genetically heterogeneous disorder caused by mutations in cardiac ion channels [1]. Patients with LQTS are predisposed to syncope, life-threatening arrhythmias and sudden death due to delayed ventricular repolarization. Clinical manifestations of LQTS are variable according to gender, age and genetic backgrounds. LQTS concurrent with lower heart rate or atrioventricular block is rare but fatal, which usually manifests itself before birth or during the neonatal period.

The mutation in *SCN5A*, which encodes the alpha subunit of cardiac voltage-gated sodium channel ($Na_v1.5$), is responsible for LQTS type3 (LQT3). As more than 150 mutations in *SCN5A* have been reported [2], several types of mutations such as P1332L and F1473C are associated with intrauterine and neonatal manifestations of LQT3 with the higher mortality [3].

We here present a notable case of a neonate with fatal LQT3 who pre- and postnatally developed atrioventricular block and ventricular tachycardia (VT). Genetic analysis demonstrated a novel *de novo* heterozygous mutation in SCN5A associated with the linker between III and IV domains of $Na_v1.5$.

2. Case report

2.1. Patient

A male newborn weighing 2334 g was delivered at 37 weeks of gestation by caesarean section because prenatal ultrasound demonstrated fetal hydrops with atrioventricular block, incessant ventricular tachycardia and decreased ventricular function. There was no maternal obstetrical or medical history. As he had poor perfusion and respiratory insufficiency, assisted ventilation and administration of dobutamine were started. Irregular and weak pulsation was noted. Chest X-ray showed that cardiothoracic ratio was 67%. Echocardiogram showed dilated left ventricle, decreased left ventricular ejection fraction (23%) and significant pericardial effusion. Electrocardiogram (ECG) demonstrated 2:1 atrioventricular block and polymorphic ventricular tachycardia (VT) (Fig. 1A). VT was refractory to intravenous administration of magnesium (50 mg/kg) and lidocaine (3 mg/kg). Although prenatal ultrasound raised the suspicion of LQTS, a definitive diagnosis was not made. To improve

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doi:10.1016/j.ijcard.2009.04.023

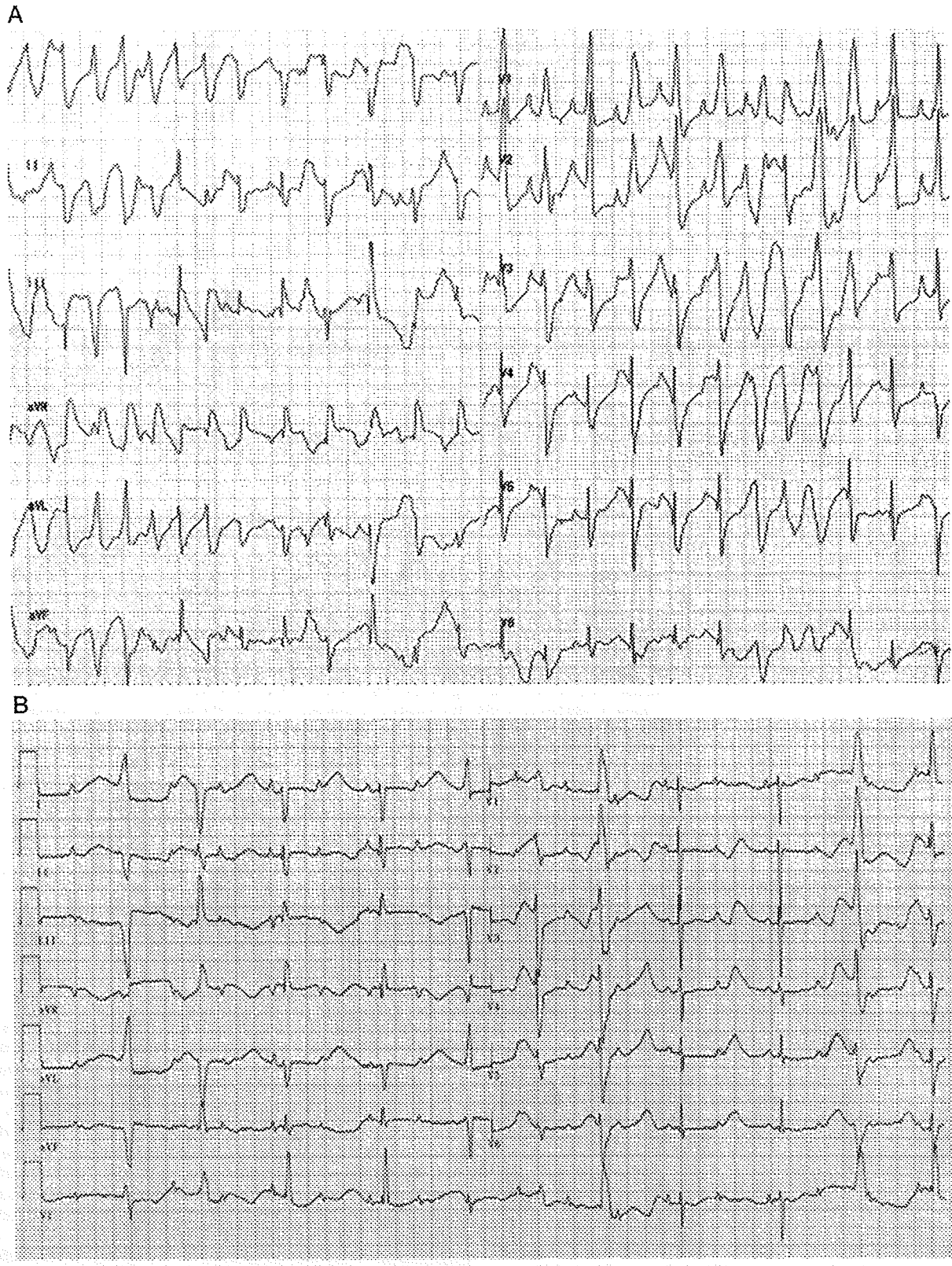

Fig. 1. Twelve-lead electrocardiogram at admission (A), and after administration of amiodarone (B). Paper speed 25 mm/s; 10 mm/1 mV. A, Polymorphic ventricular tachycardia. B, 2:1 Atrioventricular block (HR 56 bpm, atrial rate 112 bpm) due to extremely prolonged corrected QT interval (as long as 860 ms).

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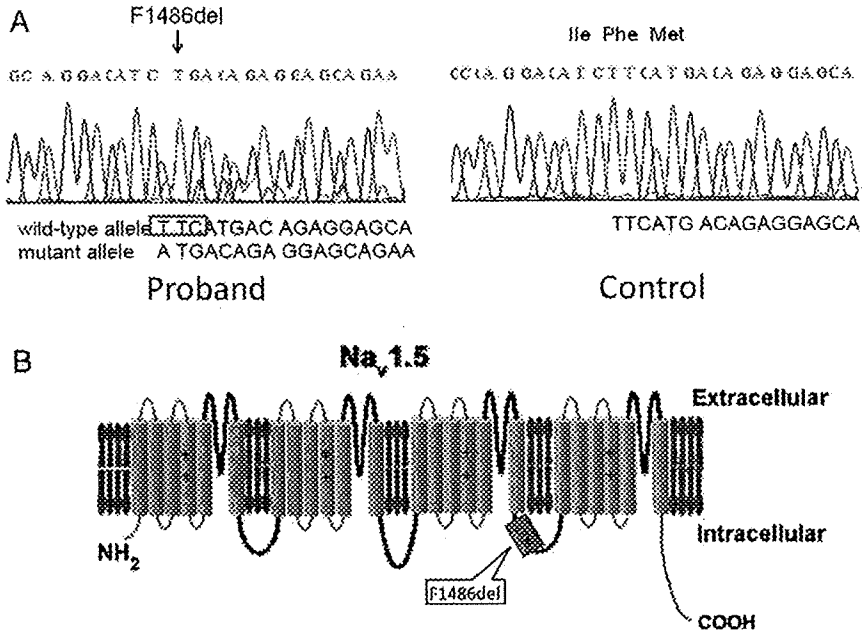

Fig. 2. A, The sequence analysis of exon 26 in *SCN5A*. A heterozygous deletion of TTC at nucleotide position 4456–4458 was detected in the proband. This nucleotide deletion was predicted to cause an amino deletion of phenylalanine at 1486 (F1486del). B, Diagrammatic representation of the human cardiac sodium channel displaying the location of the mutation identified in the present case. F1486del mutation resulted in a deletion of the amino acid in the center of IFM motif.

the circulatory instability, the patient was given a test dose of intravenous amiodarone (5 mg/kg) which resulted in termination of VT. ECG in sinus rhythm showed 2:1 atrioventricular block (atrial rate of 112 bpm and ventricular rate of 56 bpm) with an excessive QT prolongation (corrected QT interval, 860 ms) and late-appearing T wave (Fig. 1B). However, after a few minutes, ECG demonstrated VT again with following circulatory instability. Further administration of lidocaine, beta-blocker and amiodarone was ineffective. Cardiac pacing was intended to increase heart rate, but in failure. In spite of repetitive cardioversion and chest compressions, he died 18 h after birth. Autopsy was not performed.

There was no family history of prolonged QT interval, syncope, or sudden death. Both parents had screening electrocardiograms with normal QT intervals. There was no sibling.

2.2. Mutational analysis

Genetic DNA was extracted from venous EDTA blood of the present patient and his parents by standard procedure. Because of the ECG phenotype, all coding regions of *SCN5A* were first sequenced directly. Abnormal conformers were amplified by polymerase chain reaction, and sequencing was performed on an ABI PRISM 3100 DNA sequencer (Applied Biosystems, Foster City, California). A heterozygous deletion of TTC at nucleotide position 4456–4458 in exon 26 was detected in the present patient (Fig. 2A). No other mutations were detected in *SCN5A*. We have also found no mutation in *KVLQT1* and *HERG* genes. This nucleotide deletion was predicted to cause an amino deletion of phenylalanine at 1486 (F1486del, III–IV linker of Na$_v$1.5). In a large control population, this mutation was absent, making it less likely that it was a rare polymorphism. Since the mutation was not identified in both parents, we considered it to be a *de novo* mutation.

3. Discussion

We present a notable case of a neonate with fatal LQT3 who had a novel *SCN5A* mutation associated with the III–IV linker domain of Na$_v$1.5. In the present case, the corrected QT interval (860 ms) was the longest among the LQTS patients in the previous reports [1,3,4]. To our knowledge, there were only seven case reports of fetal or neonatal onset LQT3 with *SCN5A* mutations [3–9]. A neonate with F1473C mutation in III–IV linker also presented the second longest corrected QT interval (825 ms) which suggested the III–IV linker plays an important role to regulate the sodium channel function [3].

Previous reports indicate that the intracellular loop between domains III and IV of Na$_v$1.5 forms the inactivation gate [10]. A three-residue hydrophobic motif (IFM: 1485I-1486F-1487M) is an essential structural feature of the gate and serves as an inactivation particle that binds within the pore. F1486del mutation identified in the present case resulted in a deletion of the center of this hydrophobic amino acid cluster (Fig. 2B). We considered that F1486del mutation in *SCN5A* is critical to inactivate Na$_v$1.5.

The use of amiodarone was very controversial. ECG after birth was so complicated that we were unable to measure the QT interval exactly. Intravenous amiodarone might have some adverse effects, although it was described that intravenous administration of amiodarone had only little effect to QT intervals [11]. In the present case, the administration of lidocaine was unable to cease VT, although previous reports suggested the efficacy of lidocaine or mexiletine in LQT3 neonates with *SCN5A* mutations. Unfortunately, intravenous mexiletine was not available in our institute. Ruan et al. reported that the response to mexiletine varied among patients harboring different mutations in *SCN5A* [12]. It is assumed that the mutation in III–IV linker may be associated with the resistance to sodium channel blockers such as lidocaine or mexiletine.

In summary, we identified a novel *de novo SCN5A* mutation in a neonate with extremely prolonged QT interval resulting in cardiac death in the first day of life. This mutation is associated with the IFM motif in the linker between III and IV domains of Na$_v$1.5, which serves as an inactivation particle binding within the pore of sodium channels. This report demonstrates an interesting relationship between clinical phenotype and the location of the mutation and supported the importance of genetic analysis and tailored therapy in neonatal LQTS.

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Acknowledgments

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [13].

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Please cite this article as: Yamamura K, et al. A novel SCN5A mutation associated with the linker between III and IV domains of Nav1.5 in a neonate with fatal long QT syndrome. Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.04.023

P wave and the development of atrial fibrillation

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BACKGROUND Terminal P-wave inversion in lead V_1 representing left atrial overload has been considered a precursor of atrial fibrillation (AF).

OBJECTIVE The purpose of this study was to determine whether this P-wave morphologic characteristic can predict the development of AF.

METHODS Digital analysis of 12-lead ECGs was performed to enroll patients with P terminal force ≥0.06 s × 2 mm in lead V_1 from among a database of 308,391 ECG recordings. The prognostic value of ECG characteristics for developing AF was determined.

RESULTS A total of 78 patients (mean age 52 ± 19 years) with left atrial overload were chosen from among 102,065 patients in the database. During mean follow-up of 43 months, 15 (19%) patients developed AF (AF group) versus 63 (81%) patients who did not (non-AF group). No significant difference was noted between the AF and non-AF groups with regard to the area, duration, and amplitude of the P-wave terminal portion in lead V_1. In contrast, the area, duration, and amplitude of the P-wave initial portion in the same lead were significantly greater in the AF group than in the non-AF group (114.6 ± 73.0 μV × ms vs 73.1 ± 59.3 μV × ms, 42.2 ± 12.4 ms vs 35.7 ± 10.1 ms, and 94.0 ± 39.9 μV vs 68.8 ± 49.4 μV, respectively; $P < .05$ for each). Multivariate analysis confirmed that the area of the P-wave initial portion was independently associated with the development of AF (hazard ratio 4.02, 95% confidence interval 1.25–17.8; $P = .018$).

CONCLUSION P-wave initial portion in lead V_1 was an independent risk stratifier of AF development in patients with marked left atrial overload.

KEYWORDS Atrium; Electrocardiography; Fibrillation; Prognosis

ABBREVIATIONS **AF** = atrial fibrillation; **CI** = confidence interval; **ECG** = electrocardiogram; **LA** = left atrium; **RA** = right atrium

(Heart Rhythm 2010;7:289–294)

Introduction

The P wave reflects electrical depolarization of both the right atrium (RA) and the left atrium (LA). When the P wave is biphasic in lead V_1, the positive initial portion and the negative terminal portion of the P wave represent depolarization of the RA and the LA, respectively.[1,2] Morris et al[3] reported that the magnitude of the negative terminal potion of the P wave, calculated as the algebraic product of the duration and amplitude (P terminal force) in precordial lead V_1, was significantly larger in patients with various valvular heart diseases than in normal subjects. In their study, the P terminal force was associated with mitral valve area and increased LA pressure. The magnitude of the P terminal force has been shown to be associated with LA enlargement as revealed by transthoracic echocardiography.[4,5] These findings suggest that the negative terminal potion of the P wave in lead V_1 is a sign of pressure and volume overload in the LA, which may lead to structural and functional remodeling in the LA. Because atrial fibrillation (AF) often occurs and/or recurs in the remodeled LA,[6] the increased P terminal force may underlie the generation of AF. The increased P terminal force is observed not only in valvular heart diseases but also in other heart diseases, including hypertension, myocardial infarction, and cardiomyopathy.[7,8] These disorders potentially underlie the generation of AF. However, little is known about whether P terminal force occurring in those disorders is associated with a prognostic risk for the development of AF. Prolonged P-wave duration is a useful predictor of AF development.[9,10] The signal-averaged P-wave electrocardiogram (ECG) has a significant role in identifying patients who are susceptible to paroxysmal AF and in predicting the progression from paroxysmal to permanent AF.[11] Measurement of signal-averaged P-wave duration requires a dedicated system, which is not widely available in general clinical practice. In contrast, standard 12-lead ECGs can be conveniently recorded, and automatic analysis of 12-lead ECG recordings yields information to clinicians. In our university hospital, more than 300,000 ECGs obtained from more than 100,000 patients are available for digital analysis. Using this large database, we performed a retrospective cohort study to investigate whether terminal P-wave inversion in lead V_1 predicts the development of AF.

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1547-5271/$ -see front matter doi:10.1016/j.hrthm.2009.11.012

Methods

Database

We constructed a database for analyzing resting 12-lead ECGs recorded in our hospital, which is associated with the Shiga University of Medical Science. A total of 102,065 patients (49,286 females and 52,779 males) who had undergone ECG recordings between January 1983 and October 2008 were collected in our database, and a total of 308,391 ECG recordings were performed during this period. Twelve leads were simultaneously acquired. The 12-lead ECG was recorded for 10 seconds at a sweep speed of 25 mm/s and calibrated to 1 mV/cm in the standard leads. ECG signals were recorded at an interval of 2 ms (i.e., 500 Hz). Digital data were stored on a computer server with 12-bit resolution. From the database, patients who fulfilled ECG criteria of LA overload were chosen using the analysis software MUSE7.1 (GE Marquette Medical Systems, Inc., Milwaukee, WI, USA). Computer-processed ECGs defined LA overload criteria as follows. (1) ECGs displaying biphasic P wave in lead V_1 were chosen. (2) The P wave was divided into the positively deflected portion in the initial P wave and the negatively deflected portion in the terminal P wave. (3) The terminal P wave in lead V_1 with duration $\geq$0.06 second and amplitude ≤ -0.2 mV (i.e., P terminal force $\geq$0.12) was considered as meeting LA overload criteria in this study (Figure 1).

Study participants

From our database, 78 participants who had marked LA overload were selected and assessed for the development of AF. A control group of 234 participants who did not have LA overload also was selected (1:3 matching). Individual matching was performed accounting for confounders (age, gender, date when ECG was taken), and when control candidates numbered more than three, the three controls were chosen randomly from among the candidates. The research protocol was approved by the Ethical Committee of Shiga University of Medical Science (19-75).

Digital analysis of ECG

The MUSE7.1 software detected identical P waves using a template matching technique. A point that had an area $\geq$160 μV/ms from the baseline level was considered to be P-wave onset, and a point that had an area $\leq$160 μV/ms from the baseline level was considered to be P-wave offset. The duration, amplitude, and area of total P wave, initial P wave, and terminal P wave in lead V_1 were measured using matrix parameters available in MUSE7.1. P-wave area was constructed by integrating the duration and amplitude. Duration $\times$ amplitude of P-wave initial and terminal portions in lead V_1 were calculated as force values. These variables were composed using the average value of the P wave during 10 seconds of recording time. Because all measurements of 12-lead ECGs were performed digitally using MUSE7.1, neither intraobserver nor interobserver variability occurred in this study.

Statistical analysis

The occurrence of AF was set as an endpoint, and the prognostic factors for developing AF were explored in the analysis. Patients whose ECG exhibited AF during the follow-up period (AF group) were compared with patients who did not (non-AF group). The follow-up period was defined as the interval between the first day when an ECG with LA overload was recorded and the first day when an ECG displaying AF was recorded in the AF group, or the interval between the first day when an ECG with LA overload was recorded and the latest day when an ECG was recorded in the non-AF group. The occurrence of death from any cause during the follow-up period was assessed by mail questionnaire. Written informed consent was obtained from all patients. Data are given as mean $\pm$ SD or percentage, and group comparisons were made using t-test or Mann-Whitney test, as appropriate. Categorical variables were compared using the Fisher exact test. Comparison of AF occur-

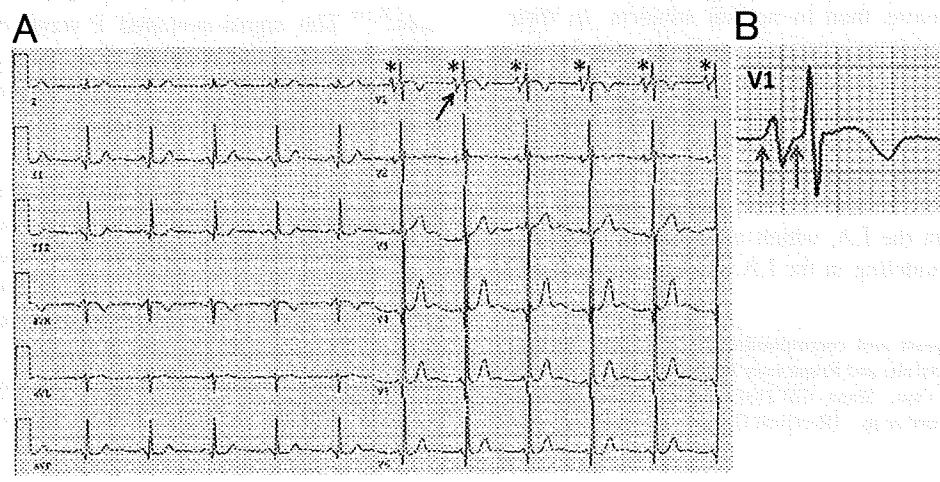

Figure 1 **A:** Twelve-lead ECG showing typical pattern of left atrial overload in lead V_1. *Red arrow* indicates P-wave negative terminal portion in lead V_1. *Asterisks* indicate P waves with identical morphology detected by template matching. **B:** Magnified ECG trace of lead V_1. *Blue arrow* indicates P-wave onset. *Green arrow* indicates P-wave offset.

rence between patients with LA overload and control patients was performed by logistic regression analysis and reported as odds ratio with 95% confidence interval (CI). Kaplan-Meier curves were used for determining the difference between two groups, and log rank test was used for examining the difference. Cox proportional hazard regression was used to estimate multivariate adjusted hazard ratios accounting for confounders (age, sex, cause of heart disease, ECG variables of P wave). All statistical tests were two-tailed, and $P < .05$ was considered significant.

Results

Atrial fibrillation

A total of 78 patients (mean age 52 ± 19 years) who fulfilled ECG criteria of marked LA overload were selected from our database using the GE Marquette 12SL ECG analysis program and enrolled for ECG analysis in this study. Of these patients, 15 (19%) developed AF (AF group), whereas 63 did not present AF (non-AF group). The control group consisted of 234 patients who were well matched for age (52 ± 19 years) and gender (78 women and 156 men; Table 1). AF developed in 3 (1.3%)of 234 control patients. The incidence of AF in patients with marked LA overload was 15-fold higher than that in control patients ($P < .001$). The odds ratio for occurrence of AF in patients with LA overload compared with control patients was 18.3 (95% CI 5.15–65.3). The mean follow-up period of the control patients was significantly longer than that of the patients with LA overload (78 ± 73 months vs 43 ± 52 months; $P < .001$). Kaplan-Meier survival analysis is shown in Figure 2. The AF-free event rate was significantly higher ($P < .001$) in patients with LA overload than in control patients (hazard ratio 24.5, 95% CI 7.94–107.3).

Characteristics of the patients

The clinical characteristics of patients in the AF and non-AF groups are listed in Table 2. The mean follow-up period of the AF group and non-AF group averaged 45 ± 61 months and 43 ± 50 months, respectively ($P = .93$). No significant difference with regard to age and sex was disclosed between the AF and non-AF groups. The average age at ECG documentation of AF was 59 ± 13 years. In the AF group, 14 (93%) of 15 patients had structural heart diseases such as hypertension, myocardial infarction, valvular heart diseases, and nonischemic cardiomyopathy. In contrast, structural heart disease was present in 46 (73%) of 63 patients in the non-AF group ($P = .081$). The presence of hypertension was more frequent in the AF group than in the non-AF

Table 1 Comparison of characteristics of control patients and patients with left atrial overload

	Control	Left atrial overload
No. of patients	214	78
Age (years)	52.4 ± 19.3	52.4 ± 19.3
Male [n (%)]	156 (66.7)	52 (66.7)
Follow-up period (months)	78.0 ± 72.9*	43.3 ± 52.0

Values are given as mean ± SD unless otherwise indicated.
*$P < .001$ vs patients with left atrial overload.

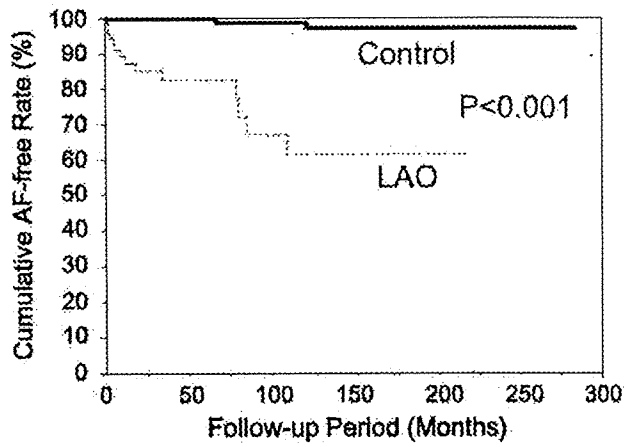

Figure 2 Kaplan-Meier estimates of atrial fibrillation (AF)-free event rate in patients with left atrial overload (LAO) and control patients. The difference between the two groups was significant ($P < .001$ by log rank test).

Table 2 Characteristics of the patients

Characteristic	AF group (n = 15)	Non-AF group (n = 63)	P value
Age (years)	55.8 ± 14.7	51.6 ± 20.3	.22
Gender (male/female)	10/5	42/21	1
Structural heart disease	14 (93)	46 (73)	.063
Hypertension	9 (60)	20 (31)	.045
Valvular heart disease	7 (47)	16 (25)	.12
Myocardial infarction	0 (0)	8 (13)	.06
Nonischemic cardiomyopathy	3 (20)	15 (24)	.66
Hypertrophic cardiomyopathy	3 (20)	7 (11)	.38
Dilated cardiomyopathy	0 (0)	8 (13)	.06
NYHA functional class I/II/III/IV	13/2/0/0	30/28/5/0	.80
Left ventricular ejection fraction (%)	63.2 ± 9.89	54.0 ± 18.5	.04
Antiarrhythmic drug			
Class IA	6	2	.01
Class IC	1	1	.32
Class III	1	0	.07
Diuretic	5	21	.70
Beta blocker	5	9	.32
Calcium antagonist	2	14	.44
Angiotensin II receptor blockade	1	2	.55
Angiotensin-converting enzyme inhibitor	3	8	.48
Nitrate	3	11	.81
Digitalis	5	15	.37
Oral anticoagulant	5	11	.14
Aspirin	3	5	.20

Values are given number, number (%), or mean ± SD.
AF = atrial fibrillation; NYHA = New York Heart Association.

group (odds ratio 3.2, 95% CI 1.01–10.3; $P = .04$), but other structural heart diseases showed no significant difference between the two cohort groups. Of note, the prevalence of both hypertension and valvular heart disease was significantly higher in the AF group (4/15 [26.7%]) than in the non-AF group (3/63 [4.8%]; odds ratio 7.3, 95% CI 1.4–37.1; $P = .018$).

Characteristics of ECG

ECG characteristics are listed in Table 3. No significant difference with regard to heart rate and frontal plane P-wave axis was seen between the AF and non-AF groups. The total duration of P wave in lead V_1 was significantly longer in the AF group than in the non-AF group. In contrast, the total amplitude (amplitude from top to bottom level) of the P wave in lead V_1 was not significant between the two groups.

For the two cohorts, we first evaluated the P-wave terminal portion in lead V_1, which was assigned as a marker for choosing patients from the database in the study. Table 4 (top) lists measurements of the P-wave terminal portion in lead V_1. The area of the P-wave terminal portion did not differ between the AF and non-AF groups. Neither the duration nor the amplitude of the P-wave terminal portion was different between the AF and non-AF groups. The same was true for the P-wave terminal force between the two groups. Because no significant difference in P-wave terminal portion in lead V_1 was observed between the AF and non-AF groups, we then estimated the initial portion of P wave in lead V_1. Table 4 (bottom) lists measurements of the P-wave initial portion in lead V_1. The area of the P-wave initial portion was significantly larger in the AF group than in the non-AF group. The duration of the P-wave initial portion was significantly longer in the AF group than in the non-AF group, and the amplitude of the P-wave initial portion was significantly higher in the AF group than in the non-AF group. Therefore, the P-wave initial force was significantly greater in the AF group than in the non-AF group.

AF development

Based on the significant association of the P-wave initial portion in lead V_1 with AF development, the AF-free event rate was estimated according to the area of P-wave initial portion. Using receiver operating characteristic analysis, the sensitivity and specificity of P-wave initial portion in response to developing AF were maximized by the area of P-wave initial portion of 65 (relative risk 4.0, 95% CI 1.2–13.1). Kaplan-Meier life-table analysis is shown in Figure 3. The area of the P-wave initial portion was associated with a significant difference of AF-free event rate between patients with area of P-wave initial portion ≥65 (n = 39) and those with area of P-wave initial portion <65 (n = 39; hazard ratio 4.02, 95% CI 1.25–17.8; $P = .02$). The rate of use of Class I antiarrhythmic drugs was identical between patients with area of P-wave initial portion ≥65 and those with area of P-wave initial portion <65 (10% vs 8%; $P = .72$). Because age is an important factor affecting the development of AF, the AF-free event rate was compared between patients <65 years old (n = 55) and those ≥65 years (n = 23). No significant difference was seen with regard to age (hazard ratio age ≥65 years to age <65 years = 2.39, 95% CI 0.72–7.19; $P = .12$). The AF-free event rate between patients with and those without hypertension was compared because hypertension was more prevalent in the AF group than in the non-AF group, but the presence of hypertension did not significantly affect the development of AF (hazard ratio of presence to absence of hypertension = 1.4, 95% CI 0.4–4.4; $P = .54$). In addition, no significant gender difference was found with regard to the AF-free

Table 3 Characteristics of ECG

Measurement	AF group	Non-AF group	*P* value
Heart rate (bpm)	69.0 ± 22.4	84.1 ± 19.3	.99
P-wave axis (°)	60.5 ± 20.5	61.9 ± 14.3	.62
P wave (ms) in lead V_1			
Total duration (ms)	126.7 ± 14.8	115.8 ± 16.7	.012
Total amplitude (μV)	310.7 ± 15.8	302.9 ± 64.9	.33

Table 4 Measurements of P wave in lead V_1

Measurement	AF group	Non-AF group	*P* value
Terminal Portion			
Duration (ms)	84.5 ± 15.0	80.1 ± 12.5	.123
Amplitude (μV)	−216.7 ± 20.1	−234.0 ± 40.0	.108
Area (μV × ms)	468.2 ± 155.0	477.7 ± 139.5	.41
Terminal force (s × μV)	18,491 ± 5,149	18,779 ± 4,584	.42
Initial Portion			
Duration (ms)	42.2 ± 12.4	35.7 ± 10.1	.018
Amplitude (μV)	94.0 ± 39.9	68.8 ± 49.4	.035
Area (μV × ms)	114.6 ± 73.0	73.1 ± 59.3	.011
Initial force (s × μV)	4,346.7 ± 2,712	2,650.3 ± 2,375	.0089

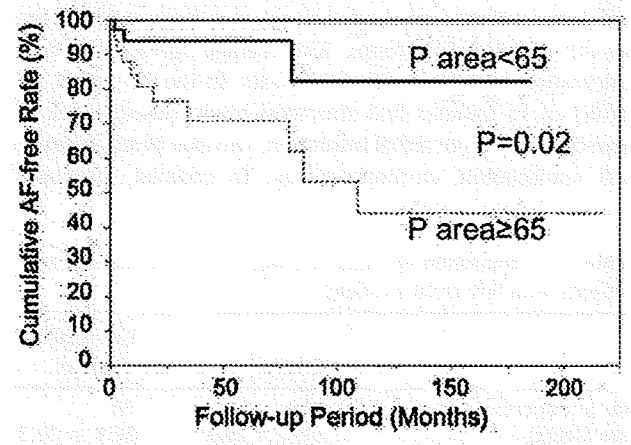

Figure 3 Kaplan-Meier estimates of atrial fibrillation (AF)-free event rate in patients with left atrial overload according to the area of P-wave initial portion in lead V_1. The AF-free event rate in patients with area of P-wave initial portion ≥65 μV × ms was significantly lower than in those with area of P-wave initial portion <65 μV × ms ($P = .02$).

Table 5 Probability of AF development during follow-up based on clinical and ECG variables

	Hazard ratio	95% Confidence interval	*P* value
P area ≥65 μV × ms	4.07	1.16–19.4	.02
P area <65 μV × ms	1	—	—
Age ≥65 years	1.96	0.56–6.18	.28
Age <65 years	1	—	—
Hypertension	0.91	0.27–3.09	.87
No hypertension	1	—	—
Male	0.79	0.23–2.88	.71
Female	1	—	—

AF = atrial fibrillation; ECG = electrocardiographic.

event rate (hazard ratio of male to female 1.0, 95% CI 0.3–3.3; $P = .99$).

Multivariate analysis confirmed that the area of P-wave initial portion was independently associated with an increased propensity for development of AF (Table 5). After adjustment for age and gender, the hazard ratio for AF development was 4.07 (95% CI 1.16–19.4; $P = .02$). The level of the area of P-wave initial portion in lead V_1 was compared in patients with and those without hypertension. The area of P-wave initial portion in lead V_1 was not significantly different between patients with and those without hypertension (84 ± 59 vs 80 ± 67, respectively; $P = .80$) and was not significantly different between patients ≥65 years old and those <65 years (86 ± 67 vs 79 ± 62; $P = .69$). In addition, gender was not significantly related to the area of P-wave initial portion (male 83 ± 61, female 77 ± 70; $P = .68$), nor was left ventricular ejection fraction ($R^2 = 0.00048$, $P = .86$ by linear regression analysis).

Discussion

Since the early description of an asynchrony of atrial depolarization by Reynolds,[12] several studies reported P-wave abnormality suggesting LA enlargement.[13–15] In 1964, Morris et al[3] advanced this concept as representing LA overload. They proposed that P terminal force >0.04 second in duration and >0.1 mV in depth at lead V_1 was associated with hemodynamically strained LA in various valvular heart diseases. Since then, increased P terminal force in lead V_1 has been considered a probable precursor to development of AF, as patients with such disorders likely suffer from AF. In this study, we systematically tested in a large size of population the hypothesis that P wave with LA overload is linked to the development of AF. Consistent with previous epidemiologic studies,[16,17] AF occurred in a few percentage of control patients in this study but occurred at a substantially higher incidence in AF patients with LA overload. Our results confirmed that when LA overload was present, the magnitude of overload in the RA could be independently attributed to the development of AF, indicating that analysis of P wave in lead V_1 deserves consideration for predicting AF. This is an important for clinicians. The measurements of P wave in our study were performed using 12-lead ECG recordings, which are commonly available in clinical practice. Moreover, computer-based measurements were performed at high resolution for data analysis of P-wave variables, which provides precise reproducibility.

P wave and AF

A principal aim of this study was to establish the prognostic importance of the P wave in lead V_1. The terminal portion of the P wave in lead V_1 has been associated with electrical depolarization of the LA alone in humans[18] and in dogs.[19] Using angiocardiography, Miller and Spertus[20] showed a correlation of marked negative component in leads V_1 and V_2 with LA enlargement. Subsequently, Morris et al[3] showed a significant correlation of the magnitude of P terminal force with severity of hemodynamic abnormality. The P terminal portion in lead V_1 is composed of several factors: (1) anatomic shift of the LA to the posterior side by hemodynamic strain, (2) enlarged LA size, (3) LA hypertrophy, and (4) reduced conduction velocity in the LA.[8,21,22] These factors are also attributed to prolonged P-wave duration. We used a much larger P terminal force for patient selection in this study than did Morris et al. Therefore, it is reasonable to speculate that patients included in this study have a high probability of AF occurrence. Indeed, compatible with this assumption, patients with marked LA overload developed AF at a substantially higher rate than did control patients. This finding indicates that increased magnitude of P-wave terminal portion in lead V_1 is a useful marker for predicting the development of AF. Furthermore, in the current study, the increased P-wave terminal portion provided information on predictivity of AF when the P-wave initial portion in lead V_1 was additively estimated. Regardless of the magnitude of the P-wave terminal portion in lead V_1, however, the magnitude of the P-wave initial portion in lead V_1 was attributed to the development of AF. This finding indicates that overload in the RA may be critical to the development of AF, and atrial vulnerability to fibrillation is likely to increase when both atria are overloaded. In addition to LA overload, electrophysiologic abnormality in the RA may increase susceptibility to AF development. Although depolarization originating from the atrial septum and/or left atrium may participate in part of the P-wave initial portion, the P-wave initial portion in lead V_1 mainly represents depolarization of the RA. Thus, our data indicate the importance of evaluating whether or not the RA is overloaded when LA overload is present. Although Class I antiarrhythmic drugs were used more frequently in the AF group than in the non-AF group, the drugs were administered similarly between two groups dichotomized according to the area of P-wave initial portion, thereby indicating that overload in the RA is an independent prognostic marker of AF.

P-wave features observed in this study reflect electrophysiologic and structural remodeling of the atrium that predisposes to the development of AF. Increased P-wave duration results from either slow conduction or an enlarged atrium. The former shortens wavelength, and the latter provides a sufficient area for reentry to occur. These pathophysiologic changes are linked to the maintenance of AF.[6]

Increased intracardiac pressure of the left ventricle may cause LA remodeling, which is likely to occur in patients with structural heart disease. Disturbed transmitral blood flow due to elevated diastolic pressure in the left ventricle may induce heterogeneous distribution of the atrial refractory period. Structural remodeling, as occurs with interstitial fibrosis and connexin redistribution, causes anisotropic conduction or discontinuous propagation. In hypertrophied atrial myocytes, triggered activity, such as early and delayed afterdepolarizations, is prone to occur.[23,24] The present study showed that an increased magnitude of P-wave initial force in lead V_1 was associated with a higher rate of AF development. This finding suggests that when a substrate develops in the RA in addition to the LA, susceptibility to the development of AF may increase.

Study limitations

Because the retrospective cohort study was conducted using ECGs recorded in our hospital, several limitations are inherent. First, we determined AF development by reviewing past ECGs, but recordings of AF might have been missed if AF terminated spontaneously before the ECGs were recorded in the hospital. Because no AF can be documented during follow-up of a patient who suffered from transient AF, this patient was classified into the non-AF group, and the AF-free duration appears longer than the true AF-free duration. Second, in the present study, LA overload was defined based on the P-wave terminal portion in lead V_1. Although this ECG marker is representative of LA overload, surrounding tissue of the heart (e.g., fat and lung) may affect the amplitude and area of the P-wave terminal portion in lead V_1, indicating that how precisely the P-wave terminal portion reflected LA overload might differ depending on the individual. Third, because our study included patients who underwent ECG recording in our hospital, the risk of AF in the study population undoubtedly was greater than that in the general population. Therefore, this factor should be considered when our results are extrapolated to a broader population.

Clinical implications

AF is one of the most common cardiac rhythm disorders; however, useful ECG identification of patients at greatest risk for developing AF remains the preeminent challenge to physicians who care for AF-prone patients. Assessment of signal-averaged ECGs of P wave has served as the principal noninvasive means of determining AF risk. This method, which estimates vulnerability to AF, is fundamentally based on delayed conduction, which may provide the substrate for reentry. Consistent with signal-averaged ECG, our ECG parameters also reflect interatrial conduction disturbance. Our data indicate that P-wave analysis using standard 12-lead ECG recordings could successfully detect a risk stratifier of AF. In addition, our quantitative relationship between P wave and vulnerability to AF could be exploited to define the risk of AF development and determine which patients are most likely to benefit from preventive anticoagulant therapy. Our results suggest that coexistence of overload in the RA and the LA may be useful for evaluating some patients. For example, screening patients with palpitations might provide a means for identifying those at high risk for AF development. In order to make measurement of the P wave a widely available marker for patients, improvements of the automatic algorithm for analysis of 12-lead ECGs are needed to predict AF in a timely fashion.

Acknowledgements

We thank Kahaku Emoto, Seiichi Fujisaki, and Tatsumi Uchiyama (GE Yokokawa Medical System Co.) for technical assistance.

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Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 401–405

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia

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ARTICLE INFO

Article history:
Received 8 September 2009
Received in revised form 11 January 2010
Accepted 11 January 2010
Available online 15 January 2010

Keywords:
Antipsychotics
QT prolongation
Schizophrenia
Sudden death

ABSTRACT

Many antipsychotic drugs cause QT prolongation, although the effect differs based on the particular drug. We sought to determine the potential for antipsychotic drugs to prolong the QTc interval (>470 ms in men and >480 ms in women) using the Bazett formula in a "real-world" setting by analyzing the electrocardiograms of 1017 patients suffering from schizophrenia. Using logistic regression analysis to calculate the adjusted relative risk (RR), we found that chlorpromazine (RR for 100 mg = 1.37, 95% confidence interval (CI) = 1.14 to 1.64; $p<.005$), intravenous haloperidol (RR for 2 mg = 1.29, 95% CI = 1.18 to 1.43; $p<.001$), and sultopride (RR for 200 mg = 1.45, 95% CI = 1.28 to 1.63; $p<.001$) were associated with an increased risk of QTc prolongation. Levomepromazine also significantly lengthened the QTc interval. The second-generation antipsychotic drugs (i.e., olanzapine, quetiapine, risperidone, and zotepine), mood stabilizers, benzodiazepines, and antiparkinsonian drugs did not prolong the QTc interval. Our results suggest that second-generation antipsychotic drugs are generally less likely than first-generation antipsychotic drugs to produce QTc interval prolongation, which may be of use in clinical decision making concerning the choice of antipsychotic medication.

1. Introduction

QTc interval prolongation is associated with presyncope, syncope, polymorphic ventricular tachycardia, the subtype torsade de pointes, and sudden cardiac death (Faber et al., 1994). Previous studies have indicated an increased risk of sudden cardiac death in patients treated with antipsychotics (Hennessy et al., 2002; Ray et al., 2001; Straus et al., 2004). A retrospective cohort study of 481,744 Tennessee Medicaid enrollees, of whom 1487 died from sudden cardiac death, found that current moderate-dose antipsychotic use (>100 mg of thioridazine equivalents) increased the rate of sudden cardiac death (multivariate risk ratio of 2.39), when compared with the nonuse of antipsychotics (Ray et al., 2001). A cohort study of three U.S. medical programs found that patients with treated schizophrenia had higher rates of cardiac arrest and ventricular arrhythmia than did controls (patients with glaucoma and those with psoriasis), with risk ratios ranging from 1.7 to 3.2 (Hennessy et al., 2002). A study of 554 sudden cardiac death subjects reported that the current use of antipsychotics was associated with a three-fold increased risk of cardiac death (Straus et al., 2004).

Although torsade de pointes and sudden death are rare, rate-corrected QT (QTc) prolongation serves as a risk factor for these conditions. In a study of 495 psychiatric patients receiving various psychotropic drugs and 101 healthy reference individuals, 8% of patients showed QTc prolongation (>456 ms) (Reilly et al., 2000). Advanced age (>65 years), as well as the use of tricyclic antidepressants, thioridazine, and droperidol were indicated as robust predictors of QTc lengthening (Reilly et al., 2000). High antipsychotic doses were also associated with QTc prolongation (Reilly et al., 2000). In a sample of 111 psychiatric inpatients receiving a median daily dose of more than 600 mg [chlorpromazine (CP) equivalent] of antipsychotics, 90% had schizophrenia or related psychoses, and 23% showed QTc interval of >420 ms, whereas only 2% of unmedicated controls did (Warner et al., 1996). However, there is little clinical data to aid in assessing the

Abbreviations: QTc, rate-corrected QT; 95% CI, 95% confidence interval; HPD, haloperidol; HPDiv, intravenous injection of haloperidol; RR, relative risk; ECG, electrocardiogram; SGAs, second-generation antipsychotics; FGAs, first-generation antipsychotics; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; CP, chlorpromazine; LP, levomepromazine; OR, odds ratio.

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0278-5846/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2010.01.008