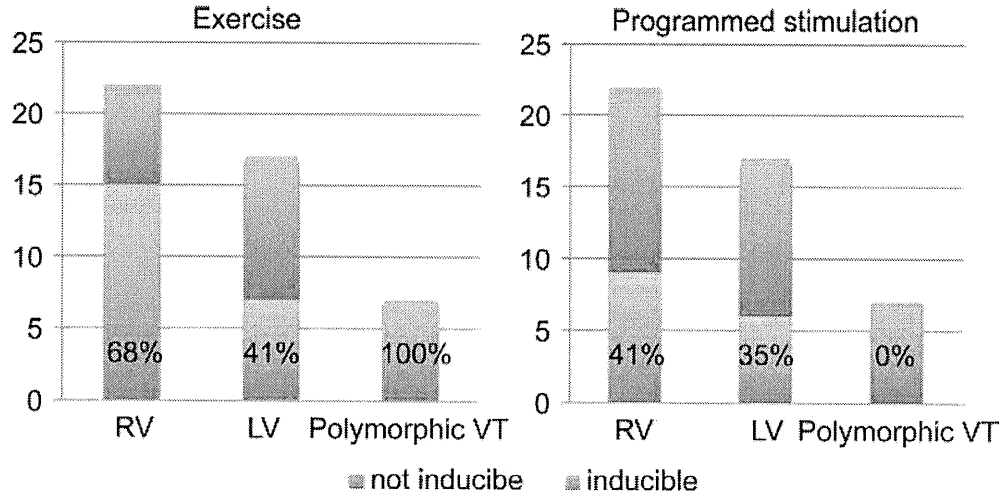

Figure 1. Induction of ventricular tachycardia (VT) by exercise and programmed stimulation. **Left panel** shows the induction of VT by exercise. **Right panel** shows the induction of VT by programmed stimulation. These panels show a comparison between VT originating from the right ventricle (RV), those originating from the left ventricle (LV) and polymorphic ventricular tachycardias.

catheters were introduced via the femoral, cervical or subclavian veins, and positioned in the right atrium, right ventricle (RV), septal leaflet of the tricuspid valve, and coronary sinus.

Programmed ventricular stimulation was performed by applying burst ventricular pacing and up to triple extra stimuli from the right ventricular apex and outflow tract in the basal state following 8 beats of ventricular pacing during 2 basic cycle lengths. If the tachycardia was not induced, programmed stimulation was repeated under an infusion of 0.01–0.03 μg/kg/min of isoproterenol. The mechanism of the VT was confirmed by the inducibility and terminability of the VT by programmed stimulation, entrainment pacing during VT, and the effects of several medications. If VT were reproducibly induced and terminated by programmed stimulation, and an entrainment phenomenon was documented, it was defined as re-entry. The VT were defined as triggered activity when the VT were induced and terminated by programmed stimulation but not reproducibly, or the VT were terminated by an injection of adenosine tri-phosphate (ATP). The VT were defined as automaticity if the VT were not induced nor terminated by programmed ventricular stimulation. The origin of the VT was suspected from the surface electrocardiograms of the VT, earliest ventricular activation, pace mapping, activation mapping using 3-dimensional electroanatomical mapping (CARTO, Biosense-Webster), and the termination point of the VT by radiofrequency ablation (RFA).

A statistical analysis was made using a Fisher's exact probability test and Pearson's chi-square test by employing JMP v 5.1 software (SAS Institute Inc, NC, USA), and a P value of <0.05 was considered statistically significant.

Results

Monomorphic VT was detected in 39 patients. Six patients had catecholaminergic polymorphic VT and 1 patient had Andersen-Tawil syndrome.

Origin of the VT

The origin of the VT was from the RV in 22 patients, and left ventricle (LV) in 17. In 21 of 22 patients with a right ventricular VT, the origin was from the right ventricular outflow tract (RVOT), the VT in the other patient was from the right ventricular apex. Left ventricular origins of the VT were observed in the left ventricular outflow tract (LVOT) in 4 patients, left ventricular apex in 7, intraventricular septum in 5, and lateral wall of the LV in one.

VT was induced by exercise tests in 68% of the right ventricular VT, 41% of the left ventricular VT, and 100% of the polymorphic VT (**Figure 1**). The exercise inducibility was higher in polymorphic VT than the RVVT and LVVT (P= 0.02).

VT was induced by programmed ventricular stimulation in 41% of the patients with right ventricular VT, 35% of those with left ventricular VT, and in none of those with polymorphic VT. There was no difference in the programmed stimulation inducibility between the RVVT, LVVT, and polymorphic VT (P=0.13).

ATP was administered during VT in 15 patients, and 9 (60%) VT were terminated by an ATP injection (**Figure 2**). The sensitivity to ATP was not different between the RVVT and LVVT (P=0.23). Verapamil was injected in 11 patients and the VT terminated in all of those patients.

Mechanism of the VT

From the results of the programmed stimulation and response to the drugs, the mechanism of the VT was suspected to be triggered activity in 36.4%, automaticity in 40.9%, and re-entry in 22.7% of the right VT. The mechanism was suspected to be re-entry in 52.9%, triggered activity in 5.9%, and automaticity in 41.2% of the left VT (**Figure 3**).

Radiofrequency Ablation

RFA was performed in 32 patients and 22 patients (69%) were successfully ablated. RFA was not performed in 5 patients because we did not start doing RFA at EPS. RFA was not performed in 9 patients after starting RFA, because no VT was induced during the EPS in 1 patient, the VT focus was very close to the His potential recording site in 1 patient,

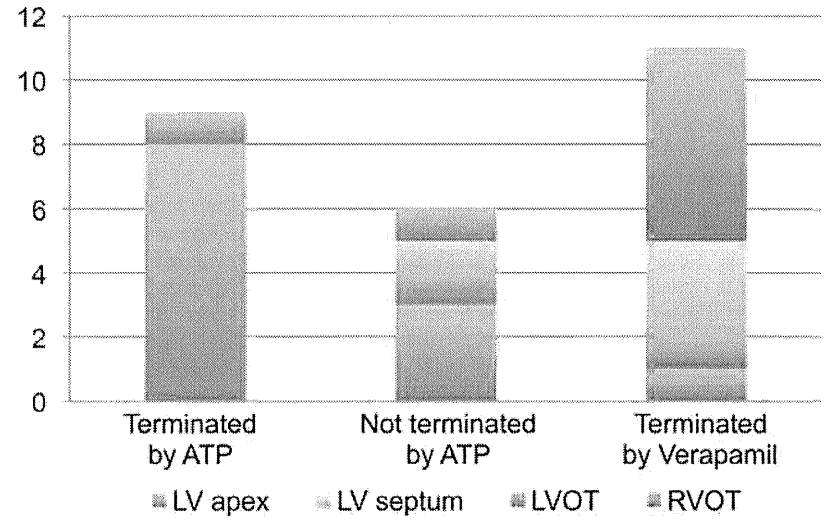

Figure 2. Effect of adenosine triphosphate (ATP) and verapamil on the ventricular tachycardia. This panel shows the effects of ATP and verapamil on the origin of the ventricular tachycardia. RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; LV, left ventricle.

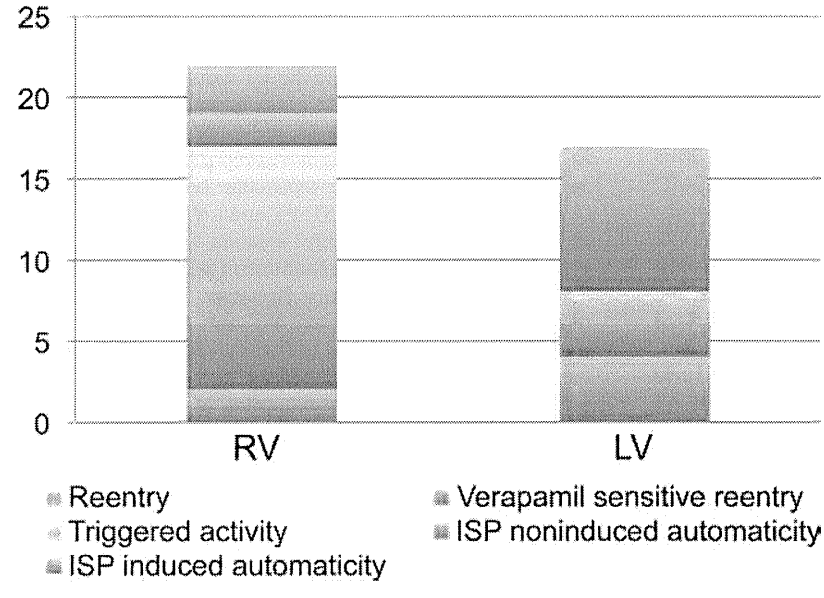

Figure 3. Suspected mechanism of the ventricular tachycardia. This panel shows that from the results of the programmed stimulation and response to the drugs, the mechanism of the ventricular tachycardia could be presumed. RV, right ventricle; LV, left ventricle; ISP, isoproterenol.

polymorphic VT was noted in 7 patients. In 12 of the automatic VT patients, 8 (67%) were successfully ablated by RFA, 1 patient was controlled with anti-arrhythmic agents, and 3 were followed without any medications; in 9 of the VT patients with triggered activity, 7 (78%) were successfully ablated by RFA, 1 patient was controlled with anti-arrhythmic agents, and 1 was followed without any medications; in 11 of the re-entrant VT patients, 7 (64%) were successfully ablated with RFA, and 4 were controlled with anti-arrhythmic agents. RFA was not performed in 7 patients with polymorphic VT, however those patients were controlled with anti-arrhythmic agents, and 2 additionally underwent implantable cardioverter defibrillator (ICD) implantation. In 7 of the 10 unsuccessful patients, RFA was performed without using a CARTO system. The reason for the failure of the ablation before using the CARTO system was as follows; the VT focus was very close to the His potential recording site (para-Hisian VT) in 2 patients, failure to initiate the VT because the mechanism of the VT was automaticity in 2 patients, and it was technically impossible to reach the ventricular focus in 3 patients. After using the CARTO system, the ablation in 2 patients with left ventricular epicardial VT, and in 1 patient with a para-Hisian VT was unsuccessful. However, the other 81% of the VT were successfully ablated.

Discussion

Most of the data from the electrophysiological findings of idiopathic VT have been obtained from adult patients.[2–5] However, relatively few data on the electrophysiological findings have been reported in pediatric patients.[1,6–8] The largest VT study in pediatric patients was reported by Pfammatter et al.[1] They concluded that most of the VT in children originated from the RVOT (70%), and the mechanisms of the VT were

enhanced automaticity or triggered activity. Throughout the past decade, several studies have been undertaken to define the clinical course and outcome in pediatric patients with idiopathic VT,[1,6–9] but the electrophysiological mechanisms have not been evaluated in detail. This study examined the detailed electrophysiological mechanisms in pediatric patients with idiopathic VT.

In another report in adult patients, up to 90% of ventricular out-flow tract VT originate from the RV, mainly from the RVOT,[10] but also from other regions of the RV, including sites above the pulmonary valve.[11] LVOT tachycardia can arise from endocardial sites, epicardial sites,[12] the area of the aorto-mitral continuity, as well as from foci accessible from the aortic sinuses of Valsalva.[13,14] In our study, 56% of the idiopathic VT originated from the RV, and 95% of those originated from the RVOT. In 2 of 4 patients with a LVOT origin, the VT originated from epicardial sites.

Most RVOT VT is sensitive to adenosine and verapamil. These findings are consistent with VT due to cyclic adenosine monophosphate-mediated triggered activity dependent on delayed after depolarizations.[15] However, it is unclear whether LVOT VT shares a similar clinical phenotype, mechanism, and electrophysiological properties as RVOT VT.

Iwai et al reported that in 122 patients with outflow tract arrhythmias in adult patients, the VT in 100 (82%) patients originated from the RVOT, and from the LVOT in 22 (18%) patients.[2] In this study, from 41% of the RVOT foci and 50% of the LVOT foci, sustained VT was inducible, and the induction of VT was catecholamine dependent in 66% of the RVOT foci and 73% of the LVOT foci. The VT was sensitive to adenosine (88% and 78% of the RVOT and LVOT VT, respectively) as well as to the blockade of the slow-inward calcium currents (70% of the RVOT and 80% of the LVOT VT) in both groups. The above data suggest that the most common arrhythmogenic mechanism was consistent with cyclic adenosine monophosphate-mediated triggered activity for both the RVOT and LVOT arrhythmias. Based on these similarities, these arrhythmias should be considered as a single entity, and classified together as 'outflow tract arrhythmias'.[2]

In the present study, the mechanisms of the LVOT VT were automaticity in 75%, and triggered activity in 25%. Furthermore, in some patients with RVOT VT, the mechanisms were verapamil sensitive re-entry and verapamil non-sensitive re-entry.

VT at a very young age is reported mostly to be exercise-related VT.[16–19] Rocchini et al reported that graded treadmill exercise testing increased the degree of the ventricular arrhythmias in 9 of 21 pediatric patients (43%).[16] In those patients, the ambulatory monitoring and exercise testing revealed an 88% and 57% incidence of VT, respectively. Deal et al reported that exercise-related symptoms were present in 9 of 24 pediatric patients (38%).[19] Of those 9 patients with a history of exercise-related VT, treadmill testing induced sustained tachycardias in 5 and non-sustained tachycardia in one. Among the 15 patients with no history of exercise- related VT, non-sustained tachycardia was induced by exercise in 1 patient. Up to 50% of the idiopathic VT in our study was induced by exercise. The mechanism of the exercise-related VT is known to be triggered activity. However, to the best of our knowledge there have been no detailed reports on the mechanism of exercise-related VT. Exercise-related VT was present in 6 of 11 patients with triggered activity associated VT (55%), 10 of 15 with automaticity associated VT (67%), and 6 of 13 with re-entry associated VT (46%) in our study. There was no difference in the mechanism of the idiopathic VT induced by exercise.

As in the adult patients, where RFA of idiopathic VT was proven to be associated with high success rates,[20] several reports on the RFA of VT in children have also shown a similar safety and efficacy of the procedure in pediatric patients. The success rate for the ablation of either right or left VT has ranged from 83 to 88%.[21–23] In this study, the radiofrequency catheter ablation was successful in 69% of the patients. Two patients with an epicardial origin were incapable of being ablated from the ventricular endocardium or the aortic sinus of Valsalva. Tanner et al reported that in 5 of 33 patients with idiopathic outflow tract VT, it was not possible to ablate the VT from the left or right ventricular endocardium or the aortic sinus of Valsalva.[24] Three patients underwent a successful ablation via a coronary venous approach and 2 by a transpericardial approach.[24] In those cases, a coronary venous approach or transpericardial approach can be successful for the catheter ablation of the VT focus. However, reports of the transpericardial approach being used in the pediatric age group are limited, and the manipulation involved in this catheter ablation might have potential risks of coronary sinus rupture and cardiac tamponade. Irrigation catheters might increase the success rate for some of the epicardium origin VT.

Three of the patients with a para-Hisian origin were unable to be ablated in this study. In those cases, cryoablation might have been useful for ablating the VT focus. However, it is still difficult to ablate the VT in patients with automatic mechanisms of the VT because of the difficulty in inducing the VT. EnSite Array mapping system was reported effective for non-sustained VT or premature ventricular contractions.[25]

In the patients with RVOT VT and LVVT, the success rate of the radiofrequency catheter ablation was fairly successful even in children, and we recommend radiofrequency catheter ablation in these patients. However, in the patients with polymorphic VT or autonomic VT, anti-arrhythmic drugs or an ICD implantation might be the first choice of treatment in these patients. The development of a smaller sized mapping system with a simultaneous recording of the onset of the VT would make it easer to ablate the autonomic or polymorphic VT in children. The development of a small sized ICD system could be of benefit for children whose VT was difficult to control ether by RFA or anti-arrhythmic drugs.

Conclusions

The exercise inducibility was higher in polymorphic VT than the RVVT and LVVT. There was no difference in the programmed stimulation inducibility between the RVVT, LVVT, and polymorphic VT. The sensitivity to ATP was not different between the RVVT and LVVT. In some patients with idiopathic VT, non-verapamil sensitive re-entry was documented, and was more common in patients with ischemic heart disease or cardiomyopathy.

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Mutation and gender-specific risk in type 2 long QT syndrome: Implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome

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BACKGROUND Men and women with type 2 long QT syndrome (LQT2) exhibit time-dependent differences in the risk for cardiac events. We hypothesized that data regarding the location of the disease-causing mutation in the *KCNH2* channel may affect gender-specific risk in LQT2.

OBJECTIVE This study sought to risk-stratify LQT2 patients for life-threatening cardiac events based on clinical and genetic information.

METHODS The risk for life-threatening cardiac events from birth through age 40 years (comprising aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) was assessed among 1,166 LQT2 male (n = 490) and female (n = 676) patients by the location of the LQTS-causing mutation in the *KCNH2* channel (prespecified in the primary analysis as pore-loop vs. non-pore-loop).

RESULTS During follow-up, the cumulative probability of life-threatening cardiac events years was significantly higher among LQT2 women (26%) as compared with men (14%; $P < .001$). Multivariate analysis showed that the risk for life-threatening cardiac events was not significantly different between women with and without pore-loop mutations (hazard ratio 1.20; $P = .33$). In contrast, men with pore-loop mutations displayed a significant >2-fold higher risk of a first ACA or SCD as compared with those with non-pore-loop mutations (hazard ratio 2.18; $P = .01$). Consistently, women experienced a high rate of life-threatening events regardless of mutation location (pore-loop: 35%, non-pore-loop: 23%), whereas in men the rate of ACA or SCD was high among those with pore-loop mutations (28%) and relatively low among those with non-pore-loop mutations (8%).

CONCLUSION Combined assessment of clinical and mutation-specific data can be used for improved risk stratification for life-threatening cardiac events in LQT2.

KEYWORDS Long QT syndrome; Pore-loop mutations; Sudden cardiac death; Gender

ABBREVIATIONS ACA = aborted cardiac arrest; **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LQTS** = long QT syndrome; **LQT2** = long QT syndrome type 2; **QTc** = corrected QT; **SCD** = sudden cardiac death

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Introduction

Long QT syndrome (LQTS) is an inherited arrhythmogenic disorder caused by mutations in several cardiac ion channel genes.[1] Clinically, LQTS is identified by abnormal QT interval prolongation on the electrocardiogram (ECG) and is associated with arrhythmogenic syncope and sudden arrhythmic death (SCD).[1,2] Type 2 long QT (LQT2), the second most common variant of LQTS, is characterized by mutations in the α subunit of the *KCNH2* channel, which conducts the rapid delayed rectifier potassium current (I_{Kr}) in cardiac myocytes.[1,2–4] Recent data show that mutations in the *KCNH2* pore-loop region, which is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk of cardiac events as compared with mutations that are located in other regions of the channel.[5,6] Furthermore, the clinical course of LQT2 patients was shown to be associated with major time-dependent gender differences, wherein women display a significantly higher risk for cardiac events than men after the onset of adolescence.[7] Prior studies in LQT2 patients, however, evaluated mainly the combined end point of any cardiac event during follow-up (comprising mostly nonfatal syncopal episodes) and did not relate gender-specific risk to mutation location in this population. Accordingly, the present study was carried out in a population of 1,166 genetically confirmed LQT2 patients from Multinational LQTS Registries and was designed to: (1) evaluate time-dependent gender differences in the risk of life-threatening cardiac events (comprising aborted cardiac arrest [ACA] or SCD) in LQT2 patients; (2) relate gender-specific risk for life-threatening events in this population to the location of the LQT2-causing mutation in the *KCNH2* channel; and (3) develop a risk stratification scheme among LQT2 patients that combines clinical and mutation-specific data.

Methods

Study population

The study population was composed of 1,166 subjects derived from (n = 263) proband-identified families with genetically confirmed *KCNH2* mutations. Patients were drawn from the Rochester, New York, enrolling center (center 1) of the International LQTS Registry (n = 761), the Netherlands LQTS Registry (n = 214), and the Japanese LQTS Registry (n = 95), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project: Denmark (n = 62), Israel (n = 24), and Sweden (n = 10). The proband in each family had otherwise unexplained diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had >1 LQTS-causing mutation (n = 11).

Data collection and management

For each patient, personal history including cardiac events, ECGs, and therapies, as well as family history, were obtained at enrollment. Clinical data were then collected yearly on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter-defibrillator (ICD), and the occurrence of LQTS-related cardic events. The QT interval was corrected for heart rate using the Bazett formula.[8] Data common to all LQTS registries involving genetically tested individuals were electronically merged into a common database for the present study.

Genotype characterization

KCNH2 mutations were identified with the use of standard genetic tests performed in academic molecular genetic research laboratories and/or in commercial laboratories. Genetic alterations of the amino acid sequence were characterized by location in the channel protein and by the type of mutation (missense, splice site, in-frame insertions/deletions, nonsense [stop codon], and frameshift).[9] The transmembrane region of the *KCNH2* encoded protein was defined as the coding sequence involving amino acid residues from 404 through 659 (pore-loop region: 548-659), with the N-terminus region defined before residue 404, and the C-terminus region after residue 659.

Pore-loop mutations disrupt normal channel gating[10] and were shown to be associated with a significantly higher risk of cardiac events as compared with mutations in each of the other regions of the *KCNH2* channel.[5,6] Accordingly, mutation location was categorized in the primary analysis of the present study as pore-loop vs. non–pore-loop. In a secondary analysis, non–pore-loop mutations were further subcategorized into those located in the transmembrane (non–pore-loop) region and in the C/N-terminus regions. Mutation type was categorized as missense vs. nonmissense. The specific mutations included in the present study, by location, type, and number of patients, are detailed in Supplementary Table 1. The distribution of study mutations in the *KCNH2* channel, by the relative number of patients, is shown in Figure 1.

End point

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising ACA (requiring defibrillation as part of resuscitation), or LQTS-related SCD (abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep). To further validate the consistency of the results among patients who received an ICD during follow-up, we also assessed a secondary end point comprising the first occurrence of ACA, SCD, or appropriate ICD shock during follow-up.

Statistical analysis

The baseline and follow-up clinical characteristics of the study population were evaluated using the χ^2 test for categorical variables, and the *t* test and the Mann-Whitney-Wilcoxon test for continuous variables. The cumulative probability of a first ACA or SCD by gender and by muta-

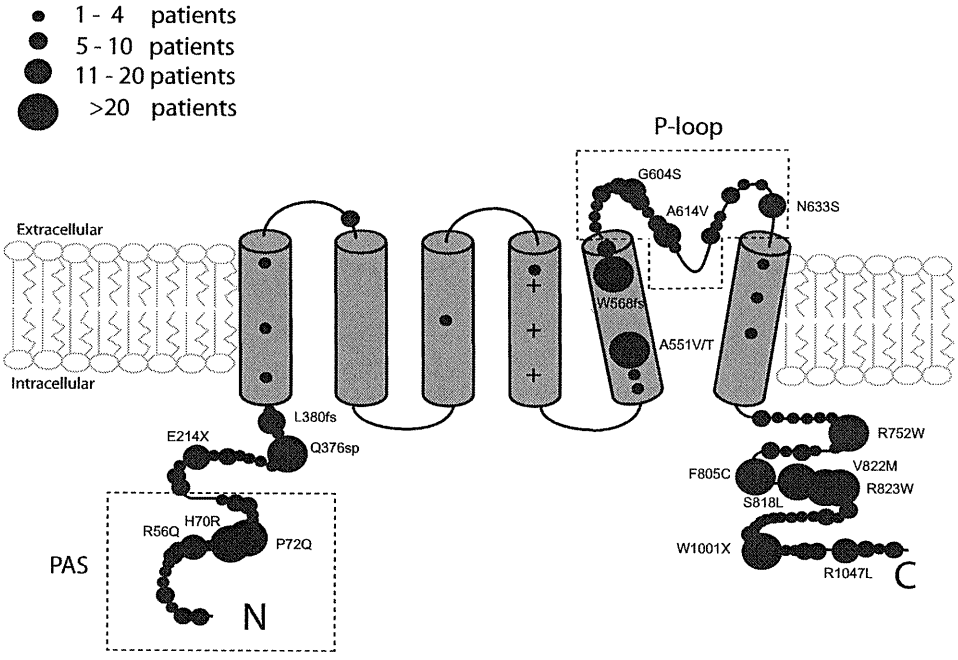

Figure 1 Distribution of mutations in the *KCNH2* potassium channel among study patients.

tion location was assessed by the Kaplan-Meier method, and significance was tested by the log-rank test. Follow-up data were censored at age 40 to avoid confounding by acquired cardiovascular disease. Multivariate Cox proportional hazards regression models were used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of ACA or SCD. Prespecified covariates in the total population model included gender, QTc duration (categorized as ≥500 ms vs. <500 ms), mutation location and type (as defined above), the occurrence of syncope during follow-up, and medical therapy with blockers. Syncope and β-blocker therapy were assessed as time-dependent covariates in the multivariate models. The effect of each covariate in male and female subjects was assessed by interaction-term analysis (i.e., by including a gender-by-risk factor interaction term in the multivariate models), with interactions tested one at a time. To avoid violation of the proportional hazards assumption due to gender-risk crossover during adolescence, we used an age-gender interaction term in the multivariate models. Patients without available baseline QTc data (n = 150) were included as a separate (QTc-missing) covariate in the multivariate models.

Using the Cox model that included interactions among gender, mutation location, QTc duration, and time-dependent syncope, covariate patterns with similar estimated hazard ratios were united to form time-dependent risk groups.

Because almost all the subjects were first- and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership.[11] All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, North Carolina). A 2-sided 0.05 significance level was used for hypothesis testing.

Results

The clinical characteristics of the study patients by gender are shown in Table 1. Baseline QTc was somewhat higher among women; however, the frequency of patients with prolonged QTc (≥500 ms) was similar in men and women. In addition, the frequency of patients with pore-loop mutations was the same in the 2 groups. During follow-up, there was no statistically significant difference between men and women in the frequency of medical therapy with β-blockers, whereas the frequency of device therapy (including pacemakers and ICDs) was significantly higher among women. The frequency of both nonfatal syncopal episodes and life-threatening cardiac events during follow-up was significantly higher among women as compared with men (Table 1).

Risk factors for ACA or SCD in the total LQT2 population

During follow-up, 179 (15%) study patients experienced the primary end point of a first ACA or SCD. Event rates were similar between men and women during childhood, whereas after onset of adolescence and during adulthood, LQT2 women experienced a significantly higher rate of ACA or SCD as compared with LQT2 men (Fig. 2). Accordingly, the cumulative probability of a first ACA or SCD from birth through age 40 years was significantly higher in women (26%) as compared with men (14%; $P < .001$ [Fig. 2]).

Table 1 Baseline and follow-up characteristics of the study population by gender

Characteristics	Male N = 490	Female N = 676	*P* value
QTc (ms)			
Continuous, means ± SD	478 ± 57	484 ± 52	.02
≥500, %	32	34	.44
RR (s), means ± SD	860 ± 250	856 ± 216	.91
Location of mutation			
Pore-loop, %	28	28	.93
Non-pore-loop:			
TM, %	4	4	.98
N-term/C-term, %	35	34	.98
Type of mutation			
Missense, %	65	68	.33
Nonmissense, %	35	32	
LQTS therapies			
β-blockers, %	52	55	.22
Pacemaker, %	3	6	.02
LSCD, %	0.6	2	.12
ICD, %	8	16	<.001
Cardiac events during follow-up			
Syncope, %	24	46	<.001
ACA, %	3	9	<.001
SCD, %	8	12	.02
Appropriate ICD shocks, %	1.5	1.9	.58
First SCD or ACA, %*	10	19	<.001

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; LCSD = left cervical sympathetic denervation; LQTS = long QT syndrome; SCD = sudden cardiac death; TM = transmembrane; QTc = corrected QT; RR = relative risk.
*Only the first event for each patient was considered.

Multivariate analysis in the total study population (Table 2) showed that during childhood (ages 0 to 13 years), the risk of ACA or SCD was similar between women and men (hazard ratio [HR] 1.53; $P = .33$), whereas after the onset of adolescence (age >13 years), women showed a significantly higher risk for ACA or SCD as compared with men (HR 2.23; $P < .001$). Mutations located in the pore-loop region of the *KCNH2* channel were shown to be associated with a significant 39% ($P = .04$) increase in the risk for ACA or SCD as compared with other ion channel mutations (Table 2). Results were similar when the secondary end point of a first ACA, SCD, or appropriate ICD shock was assessed.

Table 2 Multivariate analysis: risk factors for ACA/SCD among all LQT2 patients*

Risk factor	Relative risk		
	Hazard ratio	95% confidence interval	*P* value
Gender: female vs. male			
Age group: 0 to 13 years	1.53	0.72–3.26	.33
Age group: 14 to 40 years	2.23	1.55–3.21	<.001
Mutation location			
Pore-loop vs. non-pore-loop	1.39	1.02–1.91	.04
Pore-loop vs. C/N-term	1.44	1.06–1.97	.02
TM (nonpore) vs. C/N-term	0.91	0.45–1.87	.80
Mutation type			
Missense vs. nonmissense	0.87	0.62–1.23	.43
QTc duration (ms)			
≥500 vs. <500	3.24	2.05–5.12	<.001
Time-dependent syncope			
Syncope vs. no syncope	3.15	2.26–4.38	<.001

Abbreviations as in Table 1.
*Models were further adjusted for missing QTc values, time-dependent β-blocker therapy, and the occurrence of syncope prior to the end point (assessed as a time-dependent covariate).

Gender-specific risk factors for life-threatening cardiac events in LQT2 patients

Kaplan-Meier survival analysis showed that the cumulative probablity of ACA or SCD by age 40 years was high in women with or without pore-loop mutations (35% and 23%, respectively; $P = .02$ [Fig. 3]). In contrast, in men the rate of ACA or SCD was high among those with pore-loop mutations (28%) and relatively low among non–pore-loop mutations carriers (8%; $P < .001$ [Fig. 4]). Consistent with these findings, gender-specific multivariate analysis (Table 3) showed that the risk for ACA or SCD was not significantly different among women with or without pore-loop mutations (HR 1.20; $P = .33$), whereas men with pore-loop mutations showed a significantly higher risk for ACA or SCD as compared with

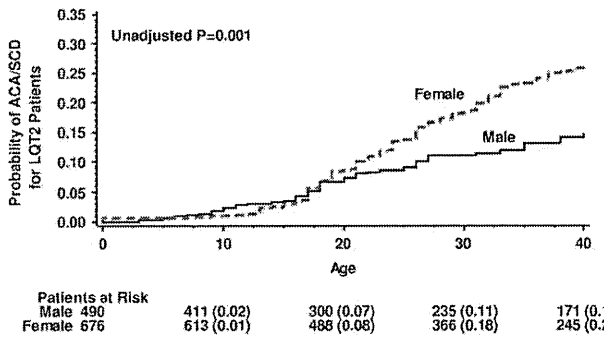

Figure 2 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 patients by gender. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

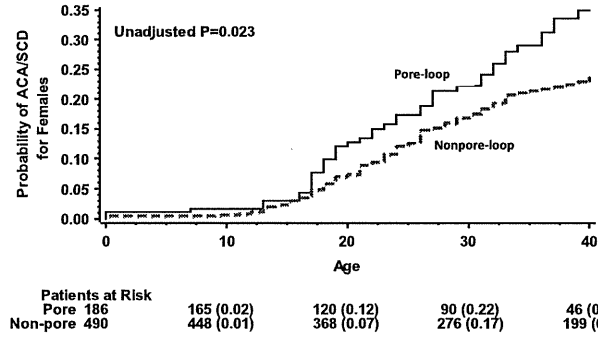

Figure 3 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 women by mutation location. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

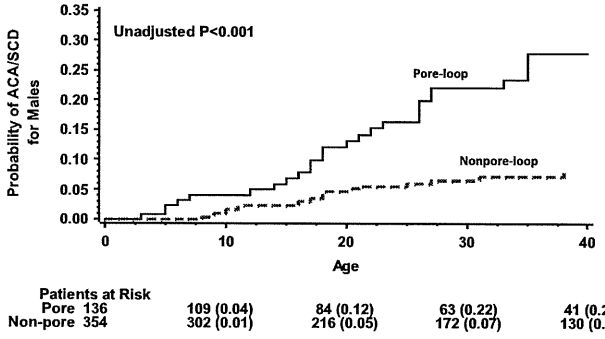

Figure 4 Kaplan-Meier estimates of the cumulative probability of a first aborted cardiac arrest or sudden cardiac death in LQT2 men by mutation location. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

men without pore-loop mutations (HR 2.18; $P = .01$). Results for both men and women were consistent when the reference group of non–pore-loop mutations was further subcategorized into the transmembrane (non–pore-loop) and C/N-terminus regions (Table 3).

QTc ≥500 ms was associated with >2-fold and >4-fold risk increase in men and women, respectively, whereas the mutation-type was not associated with a statistically significant risk increase (Table 3). Similarly, the occurrence of syncope during follow-up was associated with nearly a 3-fold increase in the risk of subsequent ACA or SCD in men, with a >3-fold risk increase in women (Table 3).

Time-dependent medical therapy with β-blockers was associated with a significant 61% reduction in the risk of ACA or SCD in the total study population (HR 0.39 [95% confidence interval 0.20 to 0.74]). The benefit of treatment with β-blockers was not significantly different between men and women (*P* value for β-blocker–by–gender interaction = 0.23).

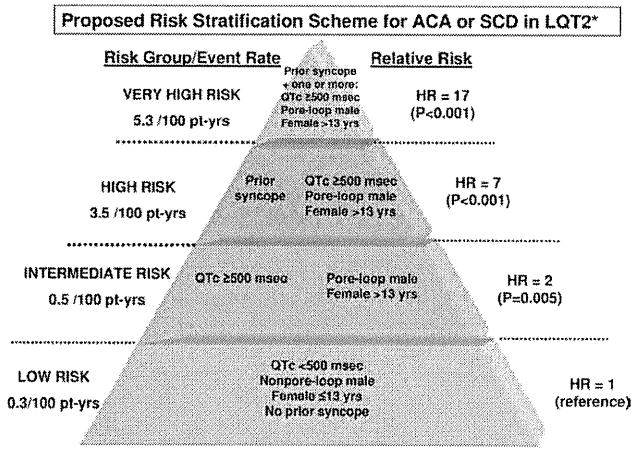

Figure 5 Proposed scheme for risk stratification for the end point of ACA or SCD in LQT2 patients by gender, mutation location, QTc, and a history of prior syncope. *Hazard ratios and score estimates were obtained from a multivariate Cox model that included interactions among the identified risk factors (categorized by QTc duration, time-dependent syncope, gender, and mutation location); decimal points in HRs are rounded to the nearest whole number; event rates per 100 person-years were calculated by dividing the number of life-threatening cardiac events (comprising ACA or SCD) in each risk category by the total follow-up time in the category (with follow-up censored after the occurrence of a ACA) and multiplying the result by 100. ACA = aborted cardiac arrest; HR = hazard ratio; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death; QTc = corrected QT.

Risk stratification for ACA or SCD in LQT2 patients

Using interaction terms among risk factors related to gender, mutation location, QTc duration, and time-dependent syncope in the time-dependent Cox models, we identified 4 risk groups with significantly different risk for the end point of ACA or SCD (Fig. 5): (1) a low-risk group, comprising LQT2 patients with no risk factors (i.e., QTc <500 ms, no prior syncope, male subjects without pore-loop mutations or female subjects ≤13 years of age); (2) an intermediate-risk

Table 3 Multivariate analysis: risk factors for ACA/SCD among LQT2 patients by gender*†

	LQT2 male subjects		LQT2 female subjects	
	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Mutation location				
Pore-loop vs. non-pore-loop	2.18 (1.28–3.72)	.01	1.20 (0.83–1.74)	.33
Pore-loop vs. C/N-term	2.04 (1.15–3.61)	.01	1.18 (0.81–1.70)	.39
TM (nonpore) vs. C/N-term	NA‡		1.25 (0.60–2.58)	.56
Mutation type				
Missense vs. nonmissense	0.56 (0.29–1.06)	.08	1.29 (0.82–1.74)	.25
QTc duration (ms)				
≥500 vs. <500	2.16 (1.08–5.06)	.03	4.05 (2.33–7.04)	<.001
Time-dependent syncope				
Syncope vs. no syncope	2.83 (1.36–5.58)	.01	3.32 (2.19–4.87)	<.001

Abbreviations as in Table 1.

*Findings were further adjusted for missing QTc values, time-dependent β-blocker therapy, and the occurrence of syncope prior to the end point (assessed as a time-dependent covariate).

†Models were carried out in the total population using interaction-term analysis, with interactions tested one at a time; all interaction *P* values were >.05.

‡Hazard ratio was not computed due to a low event rate in male patients with TM mutations.

group (HR vs. low-risk group = 2.14; $P = .005$), including (a) male subjects with pore-loop mutations or women >13 years of age (regardless of mutation location) and no additional risk factors; and (b) patients with QTc ≥500 ms and no additional risk factors; (3) a high-risk group (HR vs. low-risk group = 7.22; $P < .001$), including (a) patients with prior syncope and no additional risk factors, and (b) male subjects with pore-loop mutations or female subjects >13 years of age with QTc ≥500 ms, but without prior syncope; and (4) a very-high-risk group (HR vs. low-risk group = 17.01; $P < .001$), comprising patients who experienced prior syncope and also had 1 or more additional risk factor (i.e., QTc ≥500 ms, male with a pore-loop mutation or female >13 years old).

The nature of time-dependent covariates precludes assessment of cumulative event rates based only on the covariate pattern at the time origin. Therefore, to obtain an estimate of event rates, we adjusted the number of events for the follow-up time in each risk group. Thus, among very-high-risk patients the rate of ACA or SCD was 5.3 per 100 patient-years; high-risk patients experienced 3.5 life-threatening cardiac events per 100 patient-years; intermediate-risk patients had an event rate of 0.5 per 100 patient-years, whereas among low-risk patients the rate of ACA or SCD was only 0.3 per 100 patient years (Fig. 5).

Discussion

The present study is the first to assess gender differences in the risk of life-threatening cardiac events in LQT2, and to relate gender-specific risk in this population to the location of the disease-causing mutation. We have shown that among patients with LQT2: (1) both men and women have a relatively low rate of ACA or SCD during childhood, whereas after the onset of adolescence and throughout adulthood women show a significantly higher rate of life-threatening events as compared with men; (2) the risk of ACA or SCD in women is high regardless of the location of the disease-causing mutation in the *KCNH2* channel, whereas pore-loop mutations identify increased risk for ACA or SCD in men; and (3) combined assessment of clinical and mutation-specific risk factors can be used for improved risk stratification for life-threatening cardiac events in patients with LQT2.

In a prior study, Zareba et al.[7] assessed age-dependent gender differences in the risk of cardiac events (comprising mostly nonfatal syncopal episodes) among 533 genotyped patients from the International LQTS Registry. The study included 209 LQT2 patients, and showed that in this population no significant gender-related differences in the risk of cardiac events were present duirng childhood, whereas in the age range of 16 through 40 years, LQT2 women had >3-fold higher risk of cardiac events as compared with men.[7] Possibly due to sample size limitations, the study did not identify a significant gender-related risk difference when the more severe end point of a first life-threatening cardiac event was assessed. The present study comprises the largest LQT2 population reported to date of 1,166 patients. We have shown that after the onset of adolescence there is a pronounced increase in the risk of ACA or SCD among LQT2 women (resulting in a cumulative event rate of 26% by age 40 years), whereas the risk of ACA or SCD among LQT2 men remains significantly lower throughout follow-up (resulting in a cumulative event rate of 14% by age 40 years). These age-gender risk differences in the clinical course of LQT2 patients may be mediated by the opposing effects of male and female sex hormones on the potassium channel. Testosterone was found to shorten the action potential duration and the QT interval through enhancement of the I_{Kr} current,[12,13] and thus may be associated with QT shortening in male subjects after childhood. In contrast, estrogen was shown to exhibit both acute and genomic effects on I_{Kr}, including reduction in channel function and prolongation of ventricular repolarization.[14,15] Thus, LQT2 women who harbor mutations impairing potassium channel activity may be specifically sensitive to estrogen activity that may result in an increase in the risk for arrhythmic events after the onset of adolesence.

Recent data from the International LQTS Registry show that the location of the mutation in the ion channel is an important determinant of arrhythmic risk in LQTS patients. In a study of 201 LQT2 subjects with a total of 44 different *KCNH2* mutations, Moss et al.[5] showed that subjects harboring pore mutations exhibited a more severe clinical course and experienced a higher frequency of cardiac events, occurring at an earlier age, than did subjects with nonpore mutations. Consistent with these findings, in a more recent study, Shimizu et al.[6] showed that mutations in the pore region were associated with a greater risk of cardiac events as compared with mutations located in other regions in the *KCNH2* channel. The pore region forms the potassium conductance pathway, and most mutations present in this region have a dominant-negative effects on I_{Kr},[10] suggesting that the pore region is critical for channel function. The findings of the present study are consistent with the previous link of high cardiac risk to pore-domain mutations, and show that the presence of pore-loop mutations was independently associated with a significant 39% increase in the risk of ACA or SCD in the total LQT2 population. Our findings, however, extend prior data and show a differential effect of mutation-related risk between LQT2 men and women. Thus, among men the presence of pore-loop mutations was associated with >2-fold ($P = .01$) increase in the risk of ACA or SCD, whereas women with pore-loop mutations did not display a significant increase in risk as compared with those with non–pore-loop mutations. Accordingly, by age 40 years the rate of life-threatening cardiac events among men with pore-loop mutations was >3-fold higher as compared with those with other mutations (28% vs. 8%, respectively), whereas the corresponding event rates among women were high regardless of mutation location (35% and 23%, respectively). Possible mechanisms that may explain the observed gender-related differences include the fact that estrogen increases I_{Kr} independently of mutation location, thereby increasing ar-

rhythymic risk even among women who carry lower-risk (nonpore) mutations in the *KCNH2* channel. In contrast, the protective effects of testosterone on I_{Kr} and ventricular repolarization in postadolescent male subjects result in a reduction in the risk of arrhytmic events among carriers of low-risk mutations, with a possible remaining residual risk in men who harbor higher-risk mutations in the functionally more important pore-loop region.

In a prior study, Priori et al.[16] proposed a risk stratification scheme for LQTS patients that is based on the LQTS genotype, QTc, and gender. This study, however, assessed a composite end point of cardiac events of any type, comprising mostly nonfatal symcopal episodes,[16] whereas the large sample size of genotyped LQT2 patients in the present study facilitated for the first time the development of a risk stratification scheme for the end point of life-threatening cardiac events within the LQT2 population. We show that combined assessment of clinical and genetic data, related to mutation location, can be used to identify risk groups of LQT2 patients with a significantly different risk of ACA or SCD and with a pronounced difference in the rate of ACA or SCD during follow-up. These findings suggest that risk stratification in LQTS should combine clinical and mutation-related risk factors that are specific for each of the 3 main LQTS genotypes.

Prior data suggest that LQT2 patients expereince a relatively high rate of cardiac events during β-blocker therapy.[17] In the present study, medical therapy with β-blockers was associated with a pronounced 61% reduction in the risk of ACA or SCD in the total LQT2 population. However, the present findings also suggest that careful follow-up, with consideration of ICD therapy for primary prevention, is warranted in high- and very-high-risk LQT2 patients. These patient subsets were shown to experience 3.5 to 5.3 events per 100 patient years (which corresponds to a high rate of 1.5 to 2.1 life-threatening cardiac events per patient from birth through age 40 years) despite frequent usage of β-blocker therapy (>80%).

Study limitations

We did not carry out expression studies to assess the effects of estrogen and testosterone on ion channel mutations by their location. Therefore, further studies are necessary to evaluate the mechanism related to the observed gender-specific risk related to mutation location.

Because of sample size limitations, we did not carry out comprehensive analysis of the relation between all function regions of the *KCNH2* channel (including the PAS, CNBD, and other C-terminus and and N-terminus domains) and gender-specific risk. However, the results from the secondary analysis in which non–pore-loop mutations were further subcategorized into mutations in the transmembrane and C/N-terminus regions support the consistency of our findings.

Conclusions and clinical implications

The present study shows a distinct association between mutation characteristics and time-dependent differences in the clinical course of LQT2 patients. We have shown that after the onset of adolescence, women with and without high-risk mutations show increased risk for life-threatening cardiac events, whereas the risk of ACA or SCD in men is increased only among carriers of the higher-risk pore-loop mutations. Thus, a comprehensive approach that combines clinical and genetic data should be used for risk assessment and management of LQTS patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.03.049.

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CLINICAL RESEARCH

Analysis of J waves during myocardial ischaemia

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Aims The aim of this study was to investigate the relationship between J-wave dynamics and arrhythmias during myocardial ischaemia in patients with vasospastic angina (VSA).

Methods and results Sixty-seven consecutive patients diagnosed with VSA by a provocation test for coronary spasm were grouped according to whether they had a J wave in the baseline electrocardiograms or not (VSA-JW group, $n = 14$; VSA-non-JW group: $n = 53$). We retrospectively studied the associations between J-wave and ST-segment dynamics and induced ventricular fibrillations (VFs) during coronary spasm. In the VSA-JW group, 7 of the 14 patients showed changes in J-wave morphology and/or gains in J-wave voltage, followed by VF in 4 patients. Compared with patients without VF, the four patients with VF showed similar maximal voltage in the baseline J waves but a higher voltage during induced coronary spasms (0.57 ± 0.49 vs. 0.30 ± 0.11 mV; $P = 0.011$). In three patients with VF, J waves progressively increased and were accompanied by the characteristic coved-type or lambda-shaped ST-segment elevations. In the VSA-non-JW group, only four patients showed new appearances of J waves during coronary spasms and another patient without a distinct J wave developed VF. Ventricular fibrillations were induced more frequently in the VSA-JW group than in the VSA-non-JW group [4/14 (29%) vs. 1/53 (2%); $P = 0.012$].

Conclusion J-wave augmentations were caused by myocardial ischaemia during coronary spasms. The presence and augmentation of J waves, especially prominent J waves with the characteristic ST-elevation patterns, were associated with VF.

Keywords J wave • ST-segment elevation • Ventricular fibrillation • Coronary spasm • Myocardial ischaemia

Introduction

The J wave is denoted by a 'notch' or 'slur' at the terminal part of the QRS complex, which may be associated with ST-segment elevation.[1,2] J waves are common in healthy individuals, and are considered to be benign;[3,4] however, prominent J waves may be observed in some clinical situations.[5–7] An association between J waves and sudden cardiac death in patients with an apparently healthy heart has been reported in cases of idiopathic ventricular fibrillation (VF)[8–11] and Brugada syndrome.[12,13] However, it is unknown as to whether J waves are associated with VF in ischaemic heart disease.

Vasospastic angina (VSA) refers to the spasm and subsequent occlusion of coronary arteries, leading to transmural myocardial ischaemia.[14] Fatal ventricular arrhythmias, including VF, may develop during spontaneous or induced coronary spasm, causing sudden cardiac death.[15–17]

In the present study, we investigated the association between J-wave dynamics and arrhythmias during coronary spasm-induced myocardial ischaemia in patients with VSA.

Methods

Study design and patients

This retrospective observational study was conducted between April 2007 and June 2010 with 114 consecutive patients who underwent a coronary spasm provocation test for the diagnosis of VSA at our hospital. All patients suffered from chest pain at rest, but no electrocardiograms (ECGs) were recorded during the incidence of chest pain. To facilitate a diagnosis, the patients underwent coronary angiography with a coronary spasm provocation test. Those patients showing bundle branch blocks, atrial fibrillation, Brugada syndrome, or Wolff–Parkinson–White syndrome were excluded.

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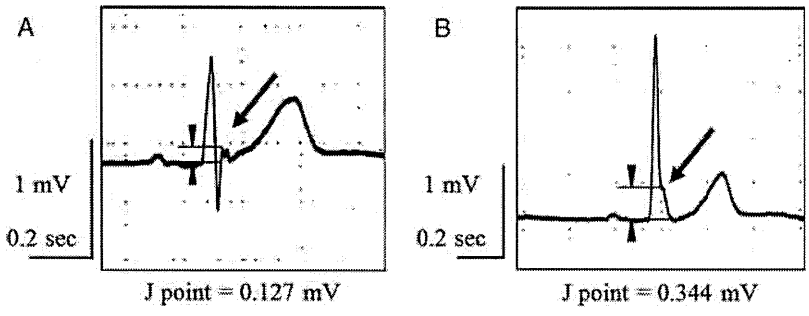

Figure 1 Electrocardiograms showing J-wave morphologies. (*A*) A notch-type J wave (arrow) is a positive deflection inscribed on the S wave. The amplitude of the J wave was measured as 0.127 mV. (*B*) A slur-type J wave (arrow) is a smooth transition from the QRS segment to the ST segment. The amplitude of the J wave was measured as 0.344 mV. The J wave was defined as positive when the J point was ≥0.1 mV above the isoelectric line ≥2 contiguous leads (arrowheads and lines).

The study protocol was approved by our institutional ethics committee. Written informed consent was obtained from all patients.

Coronary spasm provocation test

Patients underwent cardiac catheterization, which included a provocation test for coronary artery spasms. All vasodilator drugs and calcium antagonists were discontinued at least 3 days before cardiac catheterization. After the exclusion of significant stenosis, acetylcholine (ACh; Daiichi Seiyaku, Tokyo, Japan) was injected into the left coronary artery (LCA) in incremental doses of 50 and 100 μg (in 10 mL of 0.9% saline) over 20 s. Acetylcholine was then injected into the right coronary artery (RCA) as described above. If ACh did not induce coronary spasms, 50 μg of intracoronary ergonovine maleate (EM; ASKA Pharmaceutical Co. Ltd, Tokyo, Japan) was injected into the RCA and LCA over a period of 5 min.

Blood pressure monitoring and 12-lead ECGs were recorded continuously during the provocation test. Coronary spasms were verified by coronary angiography 90 s after the injection of ACh or EM. Coronary spasm was defined as total or subtotal occlusion with delayed filling of the distal segment, and was associated with chest pain and/or ischaemic ST-segment elevation on ECG. ST-segment elevation was defined as an elevation ≥0.1 mV at 40 ms after the J point in two or more leads. The site of coronary artery spasm was determined to be either the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), or RCA. The endpoint was defined as either the induction of coronary spasms or completion of the study protocol. Isosorbide dinitrate was injected to relieve spasms and/or to exclude organic coronary artery lesions. Left ventriculography was performed at the end of the study.

Electrocardiogram analysis

Standard 12-lead ECGs recorded at rest and during the provocation test for coronary spasms were scanned and magnified to 500% to measure the ECG parameters with Adobe Photoshop (version 7.0, 2002; Adobe Systems Inc., San Jose, CA, USA). The ECGs were read by two independent cardiologists blinded to the clinical characteristics and results of catheterization.

J waves were considered present when the positive deflection at the J point was ≥0.1 mV above the isoelectric line in two or more contiguous leads. The J waves were then classified as either the 'notch-type' or 'slur-type'. A notch-type J wave is a positive deflection inscribed on the S wave; in comparison, a slur-type J wave is a smooth transition from the QRS segment to the ST segment (*Figure 1*). In this study, the peak amplitude of the J wave was measured in each ECG lead presenting a J wave, and the J wave showing the highest voltage among the 12 leads was defined as the maximal J wave. Morphological changes and/or voltage gains (≥0.1 mV) were considered to be an augmentation of the J wave.

The sites of the J waves were indicated in the inferior leads (II, III, and aVF), right precordial leads (V1 and V2), left precordial leads (V3–V6), and left lateral leads (I and aVL). In this study, we analysed the presence/absence or dynamics of the J wave in all 12 leads, including the right precordial leads. Baseline ECGs indicating Brugada syndrome, which is characterized by a J-point elevation (≥0.2 mV) with a coved-type ST-segment elevation in the right precordial leads,[13] were not observed in any patients.

Data and statistical analyses

To determine whether J waves are affected by myocardial ischaemia during coronary spasms, we examined eligible patients diagnosed with VSA using the positive provocation test for coronary spasms. The J-wave prevalence at baseline was resolved, and the patients were divided into two groups: those with J waves and those without (VSA-JW and VSA-non-JW groups, respectively). Changes in the J–ST morphology and gains in the maximal J-wave voltage were then evaluated in ECGs recorded at baseline and during induced coronary spasms. We analysed the relationship between the J-wave location and coronary artery perfusion area in which the spasm was induced. When VF was induced during the provocation test for coronary spasms, serial changes in J–ST morphology were investigated.

Continuous variables are presented as the mean ± standard deviation and were compared between groups using unpaired Student's *t*-tests. Categorical variables, expressed as absolute numbers and percentages, were compared using the χ^2 test or Fisher's exact test. All statistical analyses were performed using SPSS II software (version 11.0; SPSS Inc., Chicago, IL, USA). A *P* value <0.05 was considered to be statistically significant.

Results

Induction of coronary artery spasms

Of the 114 patients, 67 (59%) were diagnosed with VSA based on a positive provocation test result for coronary spasms. Intracoronary

ACh injected into the RCA caused coronary spasms in the RCA ($n = 41$), while injection into the LCA caused coronary spasms in the LAD ($n = 23$), LCx ($n = 7$), or both ($n = 20$). Spasms in two or more vessels were induced by ACh in 30 patients. Intracoronary EM infusion was performed in 18 patients, and coronary spasms were induced in four RCAs, one LAD, and one LCx. Ergonovine maleate infusion did not provoke multi-vessel spasms. During coronary spasm, all patients complained of chest pain, and distinct ECG changes were observed. Coronary angiography demonstrated coronary spasms, which were relieved by an intracoronary infusion of isosorbide dinitrate.

Ventricular fibrillation developed following coronary spasms in five patients; three cases were caused by spasm of the RCA, and the others were caused by simultaneous spasms of the LAD and LCx. A direct-current shock was necessary to restore the sinus rhythm from VF in two of the five cases. None of the patients experienced complications related to these diagnostic catheterizations, including the provocation test for coronary spasms.

J waves at baseline

Of the 67 patients who experienced coronary spasms, 14 (21%) had J waves in their baseline ECG (VSA-JW group: 5 with notch-type and 9 with slur-type at the end of the QRS complex), while 53 patients did not have J waves (VSA-non-JW group). None of the patients had a family history of sudden death, but three patients in the VSA-non-JW group had syncopal episodes. The clinical data and baseline ECG findings were similar between patients in both groups (*Table 1*). In the VSA-JW group, J waves were located in the inferior leads in seven patients and in the left lateral leads in two patients. The remaining five patients had J waves both in the inferior leads and another site (*Table 2*). Among the baseline ECGs, none of the patients showed a J wave and ST elevation in the right precordial lead (Brugada-like ECG abnormality).

Table 1 Clinical characteristics of vasospastic-angina patients with and without J wave at baseline

Variable	VSA-JW group ($n = 14$)	VSA-non-JW group ($n = 53$)	*P* value
Age (years)	61.5 ± 8.2	63.2 ± 8.9	0.510
Male (%)	12 (86%)	40 (75%)	0.719
Syncope (%)	0 (0%)	3 (6%)	1.000
HR (bpm)	61.1 ± 12.5	65.4 ± 13.2	0.281
PQ (ms)	170 ± 37	174 ± 31	0.627
QRS (ms)	100 ± 8	101 ± 47	0.956
QRS-axis (°)	47 ± 32	40 ± 35	0.480
QT (ms)	418 ± 32	400 ± 49	0.183
QTc (ms)	418 ± 27	414 ± 49	0.765
Organic stenosis ≥75% (%)	3 (21%)	12 (22%)	1.000
LVEF (%)	63.4 ± 4.4	64.3 ± 6.7	0.627

The values are the mean ± SD or numbers (%). VSA, vasospastic angina; JW, J wave; HR, heart rate; QTc, corrected QT interval; LVEF, left ventricular ejection fraction.

J-wave dynamics during coronary spasm

J-wave augmentation during coronary spasm was noted in 7 of the 14 patients in the VSA-JW group (Patients 1–7, *Table 2*). An analysis of the J-wave location indicated that J-wave augmentation in the inferior or right precordial leads was associated with coronary spasms in the RCA, while those in the left precordial and left lateral leads were associated with coronary spasms in the LAD and LCx. The coronary spasms caused J-wave augmentations to be accompanied by ST-segment elevations in all but one case (Patient 7).

Slur-type J waves at baseline

During coronary spasm, slur-type J waves changed to notch-type J waves in four of nine patients who had slur-type J waves at baseline (Patients 1–3 and 5). Among these four patients, two patients (1 and 2) showed prominent gains in J-wave voltage accompanied by a characteristic ST-segment elevation in the right precordial leads (coved-type J–ST elevation) during coronary spasm in the RCA (*Figure 2*). On the other hand, J waves with ST elevation in the inferior leads at baseline disappeared. These notched-type J waves in the right precordial leads were morphologically similar to the coved-type J–ST elevation found in patients with Brugada syndrome. In one of the five remaining patients (Patient 4), new slur-type J waves developed with prominent gains in J-wave voltage in the left precordial and left lateral leads during spasms in the LAD and LCx (*Figure 3*). This J-wave dynamic was accompanied by a direct steep downward-sloping ST-segment elevation, with a configuration resembling the Greek character 'lambda'. Conversely, the J waves at baseline (Leads III and aVF) disappeared.

Notch-type J waves at baseline

A total of two of five patients with notch-type J waves at baseline (Patients. 6 and 7) showed no change in morphology; however, they showed an increase in the maximal J-wave voltage (≥0.1 mV).

Absence of a J wave at baseline

In 4 (8%) of the 53 patients in the VSA-non-JW group (Patients 15–18), J waves developed during coronary spasms in the RCA (notch type in 3 patients and slur type in the fourth patient) that were accompanied by ST elevation in the inferior leads.

J–ST pattern and ventricular fibrillation

In the VSA-JW group, four of seven patients with J-wave augmentation developed VF (Patients 1–4, *Table 2*). In the VSA-JW group, the occurrence of VF was more common in patients with J-wave augmentation than in those without, but it was not significant [4/7 (57%) vs. 0/7 (0%); $P = 0.070$]. Immediately after J-wave augmentation with ST-segment elevation, VF was triggered by closely coupled premature beats in all cases, which presented as left bundle branch block patterns. Of the four patients with VF, three showed progressive J-wave augmentation with a steep downward-sloping ST-segment elevation (coved-type or lambda-shaped pattern), as described above. The remaining case of VF

Table 2 Clinical and electrocardiogram data in 19 patients with a J wave at baseline or during provoked coronary spasms, and/or with ventricular fibrillation

Patient	Age (years) /sex	At baseline			During induced coronary spasm									
		Leads of J wave	Type of J wave	Voltage (mV)/lead of Max-J wave	Lead of augmented J wave	Type of augmented J wave	Voltage (mV)/lead of Max-J wave	Drug/coronary resulting in augmented J wave	Drug/ coronary resulting in coronary spasm	ST elevation	VF	Type of trigger premature beat	R-on-T pattern	Long-short sequence
VSA-JW group with an augmented J wave														
1	66/M	Inf	Slur	0.228/II	RP	Notch (coved)	0.365/V2	ACh/RCA	ACh/LAD, LCx, RCA	(+)	(+)	LBBB/NA	(+)	(+)
2	43/M	Inf, LP	Slur	0.218/aVF	RP	Notch (coved)	0.487/V1	ACh/RCA	ACh/ RCA	(+)	(+)	LBBB/LA	(+)	No
3	59/M	Inf, LP	Slur	0.105/aVF	Inf	Notch	0.141/III	EM/RCA	EM/ RCA	(+)	(+)	LBBB/NA	(+)	No
4	67/M	Inf, LP	Slur	0.404/V4	LP, LL	Slur (lambda)	1.268/V5	ACh/LCA	ACh/LAD, LCx	(+)	(+)[a]	LBBB/LA	(+)	(+)
5	64/F	Inf	Slur	0.158/aVF	Inf	Notch	0.124/III	ACh/RCA	ACh/LAD, LCx, RCA	(+)	No			
6	53/M	Inf	Notch	0.141/III	Inf	Notch	0.327/III	EM/RCA	EM/ RCA	(+)	No			
7	59/M	Inf, LL	Notch	0.218/III	LP, LL	Notch	0.467/I	ACh/LCA	ACh/LAD	No	No			
VSA-JW group without an augmented J wave														
8	68/M	Inf	Slur	0.179/III	(−)	(−)	0.141/III	(−)	ACh/LAD, RCA	(+)	No			
9	57/M	Inf	Slur	0.303/aVF	(−)	(−)	0.320/aVF	(−)	ACh/ LCx	(+)	No			
10	71/M	Inf	Slur	0.474/III	(−)	(−)	0.442/III	(−)	ACh/LAD, LCx, RCA	(+)	No			
11	75/M	LL	Slur	0.421/aVL	(−)	(−)	0.390/aVL	(−)	ACh/ RCA	(+)	No			
12	64/F	Inf	Notch	0.290/aVF	(−)	(−)	0.252/aVF	(−)	ACh/LDA, LCx	(+)	No			
13	54/M	LL	Notch	0.284/V5	(−)	(−)	0.293/V5	(−)	ACh/ RCA	(+)	No			
14	61/M	Inf, RP	Notch	0.294/V3	(−)	(−)	0.280/V3	(−)	ACh/LCx	(+)	No			
VSA-non-JW group with a new appearance of J wave														
15	63/M	(−)	(−)	0.061/III[b]	Inf	Slur	0.143/III	ACh/RCA	ACh/LAD, RCA	(+)	No			
16	63/M	(−)	(−)	0.052/III[b]	Inf	Notch	0.123/III	ACh/RCA	ACh/LAD, LCx, RCA	(+)	No			
17	47/F	(−)	(−)	0.024/III[b]	Inf	Notch	0.167/III	ACh/RCA	ACh/LAD, RCA	(+)	No			
18	60/M	(−)	(−)	0.010/aVF[b]	Inf	Notch	0.140/aVF	ACh/RCA	ACh/ RCA	(+)	No			
19[c]	64/M	(−)	(−)	0.013/aVL[b]	aVL	Notch	0.083/aVL[b]	ACh/LCA	ACh/LAD, LCx	No	(+)[a]	NBBB/NA	(+)	No

VSA, vasospastic angina; JW, J wave; M, male; F, female; Inf, inferior leads; RP, right precordial leads; LP, left precordial leads; LL, left lateral lead; Ach, acetylcholine; EM, ergonovine maleate; LCA, left coronary artery; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, circumflex coronary artery; VF, ventricular fibrillation; LBBB, left bundle branch block type; NBBB, non-bundle branch block type; NA, normal axis; LA, left axis deviation; Max-J wave, maximal J wave.

[a]A direct-current shock was needed to restore the sinus rhythm after VF.

[b]The voltage of the Max-J wave was less than the positive criteria (≥0.1 mV).

[c]Patient 19 in the VSA-non JW group developed VF during coronary spasm with an embryonic J wave only in aVL.

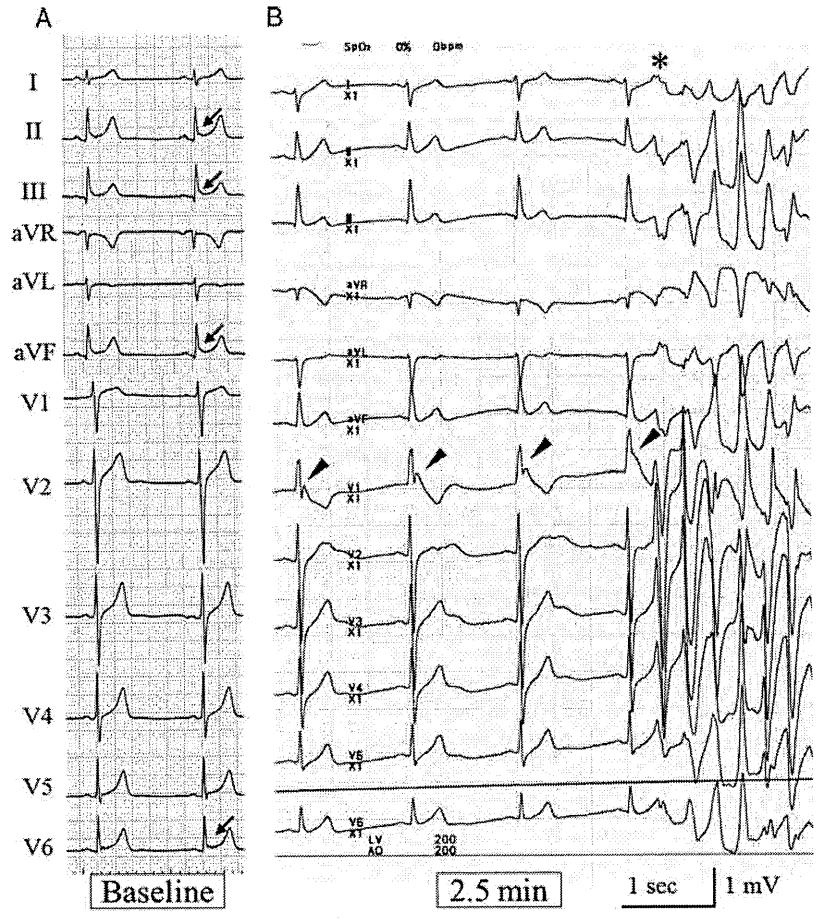

Figure 2 Electrocardiogram of Patient 2. (*A*) Baseline electrocardiogram shows slur-type J waves with ST-segment elevations in the inferior and V6 leads (arrows). (*B*) After induction of spasms in the right coronary artery by acetylcholine, these J waves became inconspicuous, while a new J wave appeared in Lead V1. This J wave increased rapidly in amplitude and changed to a coved-type J–ST elevation (arrow heads). A premature beat with a close coupling interval (*) then developed and led to ventricular fibrillation 2.5 min after intracoronary administration of acetylcholine.

was a patient who showed a change in J-wave morphology from slur type to notch type in the inferior leads during spasms of the RCA. As compared with the 10 patients who had J waves at baseline but did not develop VF, the 4 patients with VF had similar maximal J-wave voltages in their baseline ECGs (0.24 ± 0.12 vs. 0.27 ± 0.11 mV; $P = 0.984$), but reached higher voltages during the induced coronary spasms (0.57 ± 0.49 vs. 0.30 ± 0.11 mV; $P = 0.011$).

In the VSA-non-JW group, only one patient developed VF during spasms in the LAD and LCx (Patient 19). Ventricular fibrillation was preceded by an embryonic J wave, which was 0.08 mV in the Lead aVL alone (*Figure 4*). Ventricular fibrillation developed more frequently in the VSA-JW group than in the VSA-non-JW group [4/14 (29%) vs. 1/53 (2%); $P = 0.012$]. In those patients who developed VF during induced coronary spasms, intracoronary infusions of isosorbide dinitrate were administered promptly, and coronary angiography confirmed the release of the spasms. Following the resolution of VF (either spontaneously or by directed current), no recurrence was detected; the J-wave augmentations and ST elevations then gradually diminished and returned to baseline conditions.

Patient follow-up

All patients with VSA were treated with a calcium channel blocker and/or nitrovasodilator; however, none of them received antiarrhythmic agents or an implantable cardioverter defibrillator. The clinical course was uneventful during the follow-up period of 26 ± 10 months.

Discussion

J-wave prevalence

In this study, 67 of 114 patients were diagnosed with VSA based on a positive provocation test result for coronary spasms, and J waves were found at baseline in 14 (21%) of the 67 patients. Since new J

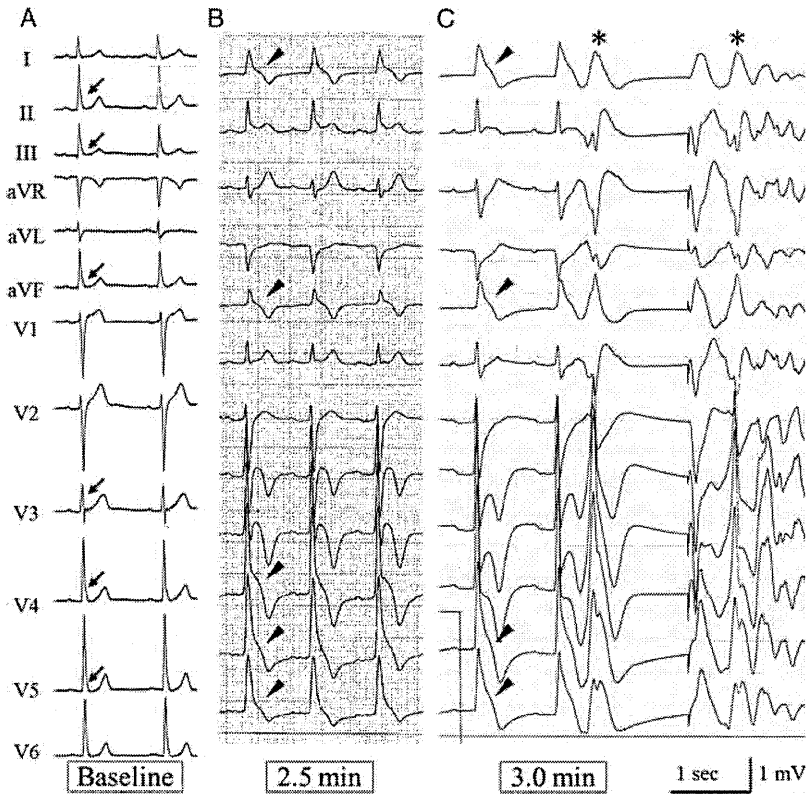

Figure 3 Electrocardiogram of Patient 4. (*A*) Baseline electrocardiogram shows slur-type J waves in the inferior and left precordial leads (arrows). (*B*) At 2.5 min after injection of acetylcholine into the left coronary artery, spasms were provoked in the left anterior descending and circumflex arteries and J waves developed in I, aVL, and V4–V6 leads (arrow heads). (*C*) These J waves were progressively augmented with a steep downward-sloping ST-segment elevation, and changed into a lambda-shaped pattern. After a long–short sequence, closely coupled premature beats (*) triggered ventricular fibrillation at 3.0 min.

waves developed during the induced coronary spasms in 4 (8%) of 53 patients, 27% of the patients with VSA [(14 + 4)/67 patients] were found to have J waves at baseline and/or in the provocation study.

In a study conducted at our hospital, J waves were found in 11.5% of the Japanese control subjects and were observed significantly more often in males than females (14.7 vs. 8.1%).[18] Although the subjects in the present study were predominantly male and might not have had entirely healthy hearts, the incidence of J waves in this study seems to be higher than that found in the general Japanese population.[18,19] Hence, the prevalence of J waves in patients with ischaemic heart disease, particularly VSA, has not been reported. To our knowledge, only some reports that Brugada syndrome showing J waves in the right precordial leads is easy to combine with VSA described an association between J waves and VSA.[20,21]

While the reason for the unexpectedly high prevalence of J waves among patients with VSA remains to be determined, we showed that in most cases VF was induced not only in patients with J waves at baseline, but also in those with J-wave augmentation during coronary spasms. Experimental studies using perfused ventricular wedge preparations revealed that the transient outward-current (I_{to})-mediated prominent action potential notch in the epicardium, but not in the endocardium, causes a transmural voltage gradient resulting in J waves on the surface ECG.[22,23] Therefore, the presence of a J wave at baseline may be related to the heterogeneous distribution of (transmural) ventricular repolarization in patients with latent myocardial ischaemia due to coronary spasm.

J-wave and ST-segment dynamics during coronary spasm

A prominent J-wave and ST-segment elevation have been reproduced in animal models of myocardial ischaemia using perfused ventricular wedge preparations.[22,24,25] Adenosine triphosphate (ATP) depletion during myocardial ischaemia causes ATP-sensitive potassium channels to open and shorten the duration of action potentials.[26–28] A cascade of pathophysiological events via ischaemia decreases the inward sodium and calcium currents. These changes lead to augmentation of the transient outward current (I_{to}), creating transmural or spatial heterogeneity of voltage gradients and resulting in J-waves and ST-segment elevations on the ECG. A voltage gradient during early acute myocardial ischaemia

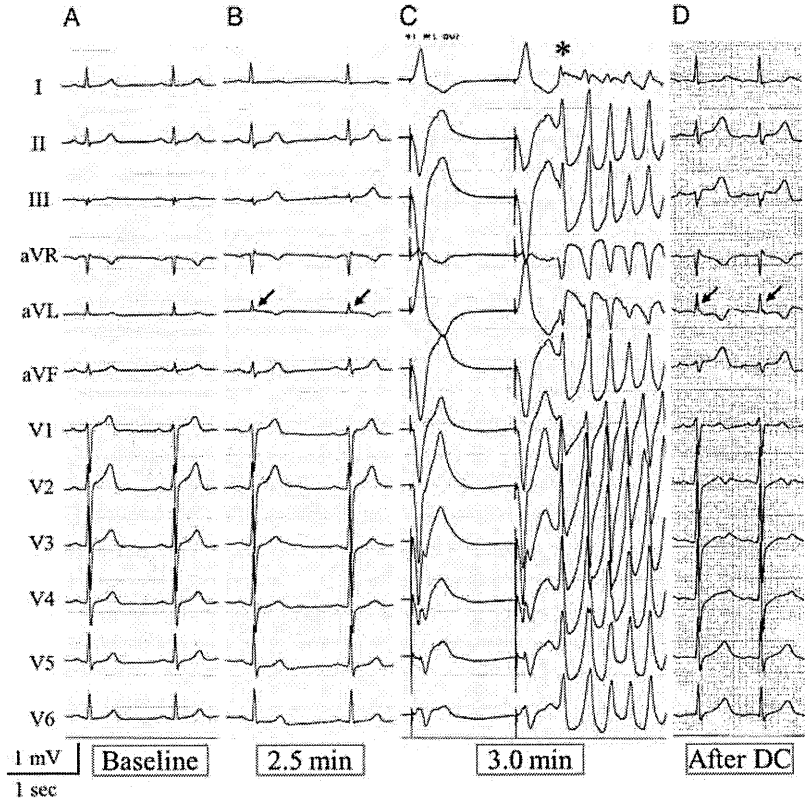

Figure 4 Electrocardiogram of Patient 19. (*A*) Baseline electrocardiogram shows no J wave. (*B*) At 2.5 min after injection of acetylcholine into the left coronary artery, spasms were provoked in the left anterior descending and circumflex arteries and an embryonic J wave (= 0.08 mV) developed only in the Lead aVL alone (arrow). (*C*) At 3.0 min, pacing beats were followed by a premature beat (*), which triggered ventricular fibrillation. (*D*) The small J wave (arrow) remained in the Lead aVL even after direct-current shock for restoration to sinus rhythm.

can produce Phase 2 reentry and subsequent VF.[25] Thus, prominent J waves with ST-segment elevation may be a warning sign for the development of VF in myocardial ischaemia as well as in Brugada syndrome.

During coronary spasm, we observed serial changes in the J waves and ST segments. Upon spasm induction, the J waves were augmented first in leads associated with ischaemic areas, followed by ST-segment elevation (including a coved-type or lambda-shaped pattern; *Figures 2* and *3*). These serial changes are in agreement with previous experimental findings.[25,29,30] We observed that (i) VF was induced more frequently in VSA patients showing a J wave at baseline and (ii) those patients who developed VF during coronary spasm showed greater J-wave augmentation than patients without VF, suggesting an association between ischaemia-induced VF and significant heterogeneity in action potentials. In addition, the finding that most cases of VF were triggered by closely coupled premature beats originating in the ischaemic area is consistent with the above mechanism of Phase 2 reentry.[25] Recently, Jastrzebski and Kukla[31] and Kukla *et al.*[32] denoted this characteristic J–ST elevation pattern as ischaemic J waves and considered it to be a warning sign for VF.

There was some discrepancy between those leads showing a J wave at baseline and those leads with an augmented J wave before the initiation of VF. For example, in Patient 2 (*Figure 2*), spasm of the RCA would cause the appearance of characteristic J-point and ST-segment elevations in the right precordial leads (coved-type ST elevation), followed by VF. On the other hand, the J waves in the inferior leads at baseline decreased and disappeared. Additionally, in Patient 4 (*Figure 3*), coronary spasms, both in the LAD and LCx, caused prominent J–ST elevation in the left precordial and left lateral leads (lambda-shaped ST elevation) due to myocardial ischaemia in parts of the anterior and lateral walls of the heart, while the slur-type J waves in Leads III and aVF present at baseline disappeared. It is reasonable to suggest that myocardial ischaemia modified the myocardial action potential configuration resulting in a larger voltage gradient through the ventricular wall and between the ischaemic and non-ischaemic myocardial lesions both in the systolic and diastolic periods of the cardiac cycle. Therefore, in those leads corresponding to the ischaemic myocardium, it is possible that the J-point and ST-segment elevation was much more obvious than the simple J-wave augmentation in these cases. On the other hand, the J waves observed at baseline (in the inferior leads in these cases) might have been concealed by the large changes in depolarization and repolarization in the surrounding myocardium during ischaemia. Since acute myocardial ischaemia due to coronary spasm

can dynamically alter both the depolarization and repolarization patterns in the heart, a J wave at baseline may either be concealed/minimized or manifested/augmented depending on the severity of myocardial ischaemia and/or segment of the coronary spasm.

Interestingly, VF developed in four of the seven patients whose J waves were augmented by myocardial ischaemia due to coronary spasms, but VF was not induced in the seven patients without J-wave augmentation. Therefore, J-wave dynamics during myocardial ischaemia are clearly more important in triggering VF than is the presence of a J wave at baseline.

In the same way that a family history of sudden death or genetic mutations bears significance in J-wave-related idiopathic VF,[12,33] it has been suggested that one's family history or the presence of a particular genetic alteration is a risk factor for primary VF during the acute phase of myocardial infarction.[34–36] Whether one's genetic background plays a role in ischaemia-induced J–ST changes or the development of VF in patients with VSA is an important question to be explored in the future.

Study limitations

This study was retrospective and included a small number of patients. However, the J-wave augmentations with a characteristic ST-segment elevation induced by myocardial ischaemia were consistent with previous reports. Because the extent and duration of myocardial ischaemia induced by coronary spasm could not be controlled in this clinical study, the effect of myocardial ischaemia on the augmentation of J waves and the development of VF might not be the same in every patient. However, three of five patients developed VF during spasm in a single vessel (the RCA); not all cases of VF were induced by multi-vessel spasms. These results imply that even extensive ischaemia did not cause VF. However, the relationship between the extent of induced ischaemia, J-wave augmentation, and the development of VF needs to be clarified.

Conclusions

This study demonstrated that myocardial ischaemia during provoked coronary spasms altered J-wave dynamics, including the augmentation and development of J waves. The presence and augmentation of J waves, especially prominent J waves with characteristic ST-segment elevations, were often associated with ischaemia-induced VF.

Conflict of interest: none declared.

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