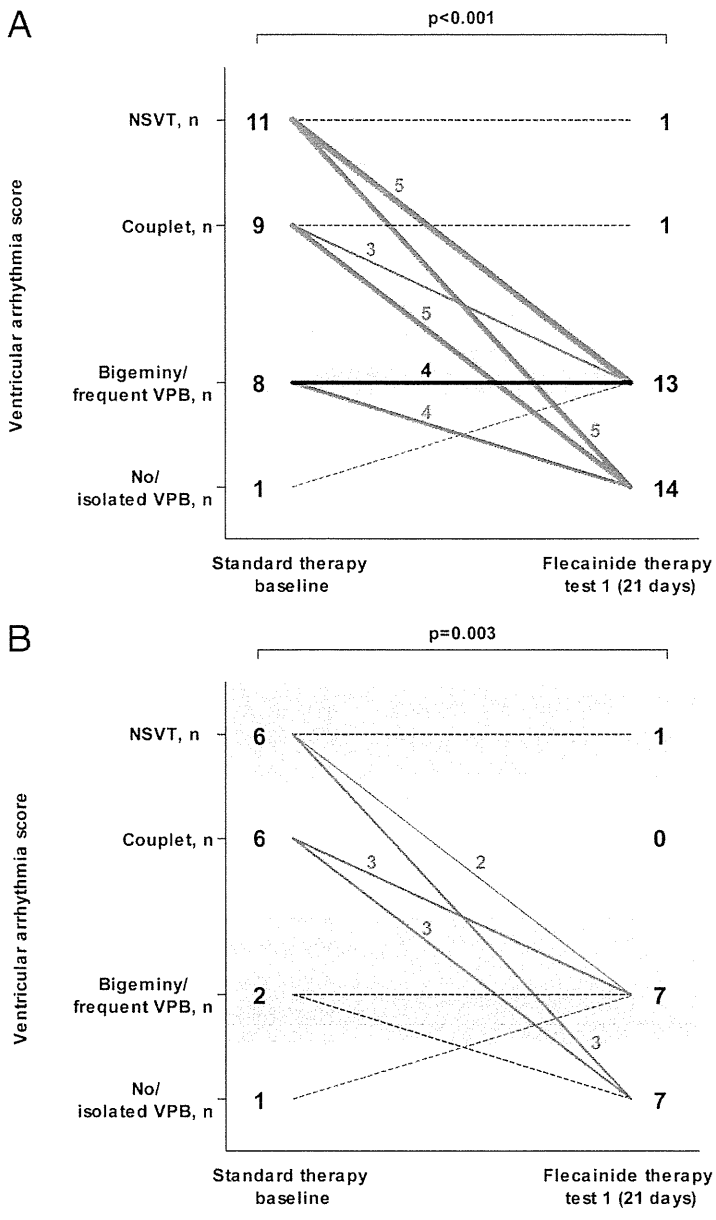

Figure 1 **Ventricular Arrhythmia Score on Standard Therapy and on Flecainide**

Ventricular arrhythmia score per patient on the baseline exercise test on standard therapy and on the first exercise test on the final (stable) flecainide dose in the entire cohort (n = 29) **(A)** and in the patients who were treated with a first-line β-blocker at an optimal dose (n = 15) **(B)**. The number of patients in each ventricular arrhythmia category and change in ventricular arrhythmia category are shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval between the 2 tests is shown. All exercise tests were performed on patients receiving an unchanged β-blocker dose. NSVT = nonsustained ventricular tachycardia; VPB = ventricular premature beats.

patients (24%) received an increased flecainide dose after the initial exercise test (Table 1). The dose increased from an average daily dose of 96 ± 28 mg to 178 ± 78 mg (range 100 to 300 mg), which resulted in a significant improvement in the ventricular arrhythmia score (Fig. 3).

Clinical follow-up. Three patients (Patients #13, #30, and #31) discontinued flecainide with <6 months of follow-up due to side effects. One patient (Patient #6) required a pacemaker because flecainide exacerbated pre-existing sinus node dysfunction. Flecainide was resumed after pacemaker implantation, and this patient was included in the study. In 2 patients (Patients #7 and #28), the stable flecainide dose was decreased because of dizziness. All other patients tolerated flecainide well without severe side effects. The β-blocker dose was decreased in 5 patients (Patients #4, #5, #6, #9, and #12) who had a partial suppression of ventricular arrhythmias on flecainide and experienced side effects of β-blocker therapy (in particular, fatigue) before flecainide

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Table 2 Exercise Test Results of the Baseline Exercise Test on Standard Therapy and on the First Exercise Test on the Final (Stable) Flecainide Dose

	Standard Therapy Baseline (n = 29)	First Exercise Test on Stable Flecainide Dose (n = 29)	p Value
Time after start flecainide, days	—	21 (5–363)	—
Sinus rate at baseline, beats/min	57 ± 10	59 ± 9	0.061
Sinus rate at maximal exercise, beats/min	145 ± 23	133 ± 18	0.002
Maximum workload attained, METs	11 ± 3	12 ± 4	0.042
Sinus rate at onset of ventricular arrhythmias, beats/min	113 ± 19	118 ± 19	0.046*
Maximum no. of VPBs during a 10-s period†	12 ± 5	5 ± 5	<0.001
Ratio of VPBs to sinus beats during the 10-s period with the maximum no. of VPBs†	1.2 ± 0.8	0.4 ± 0.4	<0.001
Isolated VPB	29 (100)	22 (76)	0.016
Bigeminal VPBs	28 (97)	13 (45)	<0.001
Frequent VPBs (>10/min)	27 (93)	14 (48)	0.001
Couplet	20 (69)	2 (7)	<0.001
Nonsustained ventricular tachycardia	11 (38)	1 (3)	0.002
Longest ventricular salvo, VPBs†	5 (3–9)	4	—
Bidirectional NSVT	4 (36)	—	—

Data are mean ± SD, median (range), or n (%). *Only the 22 patients who still had ventricular arrhythmias on the first exercise test at the stable flecainide dose were included in this analysis. †Data were available for 28 patients (not available for Patient #32).
MET = metabolic equivalent; NSVT = nonsustained ventricular tachycardia; VPB = ventricular premature beat.

was started. One patient (Patient #29) refused to take β-blockers during follow-up, with no worsening of exercise-induced ventricular arrhythmias on flecainide monotherapy.

Thus, 30 of 33 patients (91%) continued to receive flecainide and were included in the further analysis of the incidence of arrhythmic events. During a median follow-up of 20 months (range 12 to 40 months, excluding Patient #32), VT recurred in only 1 patient (Patient #1) who experienced several appropriate ICD shocks for polymorphic VT after 8 months of flecainide treatment. Her serum flecainide level was low (0.34 μg/ml) at the time of the event compared with levels obtained previously (0.75 to 0.82 μg/ml), suggesting noncompliance. She was hospitalized for 48 h, nadolol and flecainide were resumed at their previous doses, and no further ventricular arrhythmias occurred during a further follow-up of 17 months. The other 29 patients remained free of arrhythmic events during follow-up. The longest follow-up of 29 years was achieved in Patient #32, who presented with exercise-induced VT in 1981. After unsuccessful trials of multiple antiarrhythmic drugs (including mexilitine, amiodarone, propranolol, sotalol, and Ca^{2+}-channel blockers), flecainide (200 mg/day) was added to sotalol (160 mg/day), which resulted in complete suppression of ventricular arrhythmia during exercise testing. In 2008, an exercise test 48 h after stopping flecainide and sotalol showed NSVT. After restarting the combined therapy, a subsequent exercise test only showed isolated VPBs, but no VT. Subsequent genotyping revealed a mutation in the gene encoding RyR2. In Patient #33, flecainide 150 mg/day was started in 2007 because of 2 episodes of syncope with ventricular fibrillation on the ICD interrogation despite nadolol 240 mg/day. Exercise testing showed complete suppression of ventricular arrhythmias, and she has been free of arrhythmic events on flecainide for 40 months.

Discussion

Main findings. Our study demonstrates that flecainide reduces or prevents exercise-induced ventricular arrhythmias in the majority of CPVT patients receiving conventional drug therapy. These findings are important because several studies have demonstrated a significant failure rate of current drug therapy (1,3,11–16), including potentially fatal arrhythmic events in 11% of CPVT patients over an 8-year period (2). Based on our clinical experience reported here, flecainide in addition to β-blocker therapy should be considered for CPVT patients who otherwise have few alternative therapeutic options. The optimal dose appears to be between 150 and 200 mg/day (range 100 to 300 mg/day). Daily doses <100 mg were associated with a lack of therapeutic response.

Rationale for use of flecainide. CPVT is caused by mutations in the genes encoding RyR2 and cardiac calsequestrin (4,5), 2 proteins that control Ca^{2+} release from the sarcoplasmic reticulum. As a result of the mutations, Ca^{2+} is released prematurely and excessively into the cytosol under conditions of catecholaminergic stimulation, generating repetitive spontaneous Ca^{2+} waves (9,29). The increase in intracellular Ca^{2+} in turn activates the electrogenic Na^+/Ca^{2+} exchanger, which produces a transient inward current (I_{Ti}). I_{Ti} generates delayed afterdepolarizations, which can lead to triggered activity, and the initiation of ventricular arrhythmias (30). Flecainide directly targets the molecular defect in CPVT by inhibiting RyR2 channels and preventing arrhythmogenic Ca^{2+} waves (23,24). Flecain-

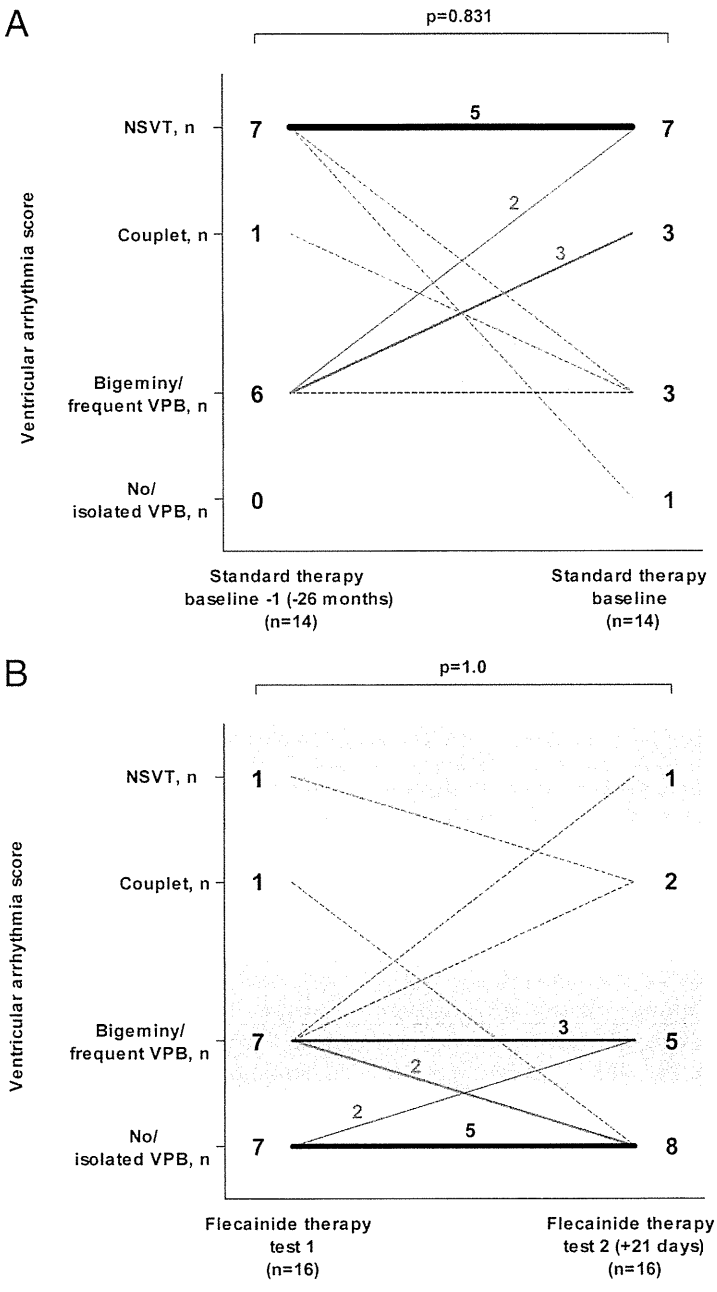

Figure 2 **Reproducibility of Ventricular Arrhythmia Score on Exercise Testing**

Ventricular arrhythmia score per patient on the baseline exercise test and on the previous exercise test at the same standard therapy dose **(A)** and on the first and second exercise tests at the final (stable) flecainide dose **(B)**. The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category are shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval between the 2 tests is shown. The standard therapy exercise tests were performed on patients receiving the same β-blocker dose with or without Ca^{2+}-channel blocker. All exercise tests on patients receiving flecainide were at the same stable flecainide dose in combination with an unchanged or lower β-blocker dose. The sinus rates at maximal exercise on the first and second exercise tests on flecainide were not significantly different (140 ± 19 vs. 144 ± 20; p = 0.245). However, the 2 patients with a ventricular arrhythmia score of 4 and 3 on the second exercise test did reach a significantly higher maximum sinus rate compared with the first exercise test (increase of 32 and 19 beats/min, respectively). Abbreviations as in Figure 1.

ide's Na^{+}-channel blockade further reduces the rate of triggered beats (23,24). This dual action could explain why flecainide is so effective in severe CPVT and provides a rationale for combination therapy with β-blockers.

RyR2-mediated sarcoplasmic reticulum Ca^{2+} release importantly regulates the beating rate of sinoatrial nodal cells (31), especially in response to catecholamines (32), and flecainide reduces the rate of spontaneous sarcoplasmic

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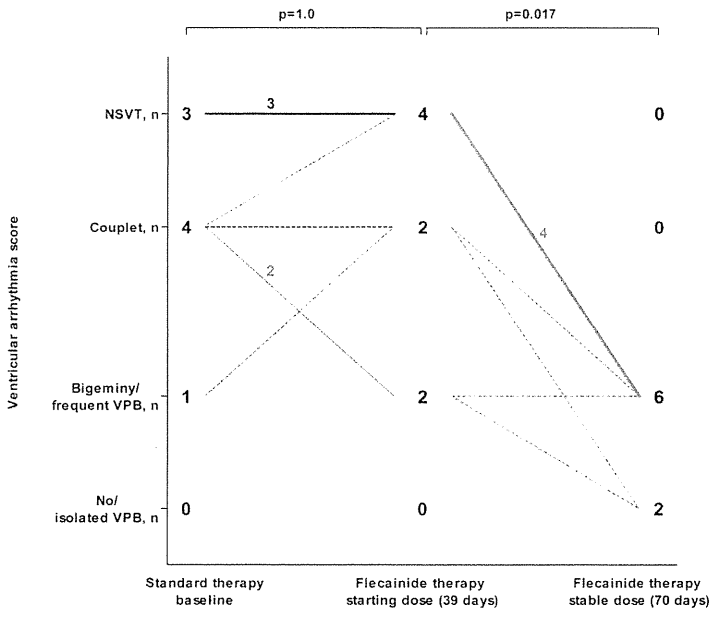

Figure 3 **Dose Dependence of Flecainide in 8 CPVT Patients Who Had an Increase in Flecainide Dose**

The number of patients in each ventricular arrhythmia category and change in ventricular arrhythmia category on the last exercise test at the flecainide starting dose (96 ± 28 mg; range 50 to 150 mg) and on the first exercise test at the final (stable) flecainide dose (178 ± 78 mg; range 100 to 300 mg) is shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval from the start of flecainide therapy is shown. All exercise tests were performed with the patients receiving an unchanged β-blocker dose. Abbreviations as in Figure 1.

reticulum Ca^{2+} release in myocytes (24). This mechanism may explain why maximum hearts rates were significantly lower in flecainide-treated patients even though workloads were higher compared with baseline exercise testing (Table 2). The reduction in sinus rate during exercise may further contribute to flecainide's efficacy in CPVT.

Clinical implications. Given the high fatality rate of untreated CPVT patients (1,2), adequate treatment is mandatory and potentially life-saving. β-blockers are considered first-line therapy. In the largest published series of patients with CPVT, the risk of cardiac arrest (defined as aborted cardiac arrest, appropriate ICD shocks, and sudden cardiac death), despite β-blocker therapy during a mean follow-up period of 8 years, was 11% (2). Others have reported very diverse fatal or near-fatal event rates despite β-blocker therapy (1,3,11–16), although the highest event rates may be explained by the predominance of (symptomatic) probands and underdosing of β-blockers. An ICD was recommended for CPVT patients who were survivors of cardiac arrest, or when syncope or sustained VT persisted despite maximum tolerable β-blockade (33). Yet, ICDs have a potentially harmful effect in CPVT patients (17,18). Moreover, many CPVT patients are children, in whom ICD implantation can lead to significant complications (34). Thus, to avoid ICD implantation and prevent ICD shocks in patients with ICDs, controlling ventricular arrhythmias is of great clinical importance. Alternative therapies are needed for CPVT patients.

Left cardiac sympathetic denervation is an effective alternative when symptoms persist despite β-blockade, but requires surgery, is not universally available, and has only been tested in small cohorts (19–22). The use of Ca^{2+}-channel blockers in addition to β-blockade has been reported to decrease ventricular ectopy in CPVT patients with continuous symptoms and/or exercise-induced ventricular arrhythmias (12,27,35), but is not effective in all patients (27,35,36). From the original 6 patients treated with verapamil and β-blockers after failure of β-blockers alone, reported by Rosso et al. (27) in 2007, 3 had clinically significant ventricular arrhythmias during 37 ± 6 months of follow-up (36). Other pharmacological agents, including Na^{+}-channel blockers, amiodarone, and magnesium, lack of efficacy in CPVT patients (1,12).

In this analysis of all consecutive patients started on flecainide at 8 international centers, adding flecainide to standard therapy was effective in further reducing exercise-induced VT and preventing arrhythmic events CPVT patients. To suppress CPVT, adequate dosing of flecainide seems critical. An increased dose may be effective when the initial dose of flecainide fails to suppress VT. Based on these results, flecainide could be added to β-blocker therapy when symptoms or either spontaneous or exercise-induced ventricular arrhythmias persist despite β-blocker.

In our young patient population with no structural heart disease, the proarrhythmic effect of flecainide as documented in patients with ischemia and impaired left ventric-

ular function (37) may not be applicable. Consistent with this hypothesis, flecainide did not cause arrhythmic events during a median follow-up of 20 months, which is longer than the mean follow-up of 10 months in the CAST (Cardiac Arrhythmia Suppression Trial). The only arrhythmic event was associated with low flecainide serum levels, suggesting that the event was due to the underdosing and not toxicity.

Study limitations. This study reports on our experience of using flecainide in a clinical setting. The number of patients is relatively small because CPVT is a rare condition and only patients without other treatment alternatives were started on flecainide. However, it is the largest evaluation of a new therapeutic strategy in CPVT patients refractory to current drug therapy, with a median of 20 months follow-up. One patient has received flecainide for 29 years with continuous VT suppression on unchanged doses, and another severely symptomatic patient has been free of arrhythmic events on flecainide for 40 months. Nevertheless, long-term follow-up in more patients would further support the clinical utility of flecainide in CPVT.

Another potential limitation is that we only quantified the effect of flecainide on exercise-induced ventricular arrhythmias, which may not accurately predict fatal arrhythmic events. However, exercise testing is clinically used to guide therapy in CPVT. In a previous study including 70 CPVT patients, exercise-induced couplets or more successive VPBs were significantly associated with future arrhythmic events (sensitivity, 0.62; specificity, 0.67) (2).

Furthermore, we cannot exclude potential bias introduced by the variability of exercise test results on unchanged treatment, as illustrated in Figure 2. Finally, in 14 patients, conventional therapy may be considered suboptimal because they received an unusual β-blocker for CPVT or a low β-blocker dose for reasons previously outlined. However, flecainide was equally effective in the subgroup of CPVT patients who were treated with a first-choice β-blocker at an adequate dose (Fig. 1B).

Conclusions

Our results suggest that flecainide is a safe and effective therapy to reduce ventricular arrhythmias in the majority of CPVT patients who have exercise-induced ventricular arrhythmias despite conventional therapy.

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Key Words: antiarrhythmia agents ■ catecholaminergic polymorphic ventricular tachycardia ■ ventricular arrhythmia.

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ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Evaluation of Transplacental Treatment for Fetal Congenital Bradyarrhythmia

– Nationwide Survey in Japan –

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Background: There are few large studies of fetal congenital bradyarrhythmia. The aim of the present study was to investigate the effects and risks of transplacental treatment for this condition.

Methods and Results: Using questionnaires, 128 cases of fetal bradyarrhythmia were identified at 52 Japanese institutions from 2002 to 2008. Of the 128 fetuses, 90 had structurally normal hearts. Among these 90 fetuses, 61 had complete atrioventricular block (CAVB), 16 had second-degree AVB, 8 had sinus bradycardia, and 5 had other conditions. The 61 CAVB fetuses were divided into those who did (n=38) and those who did not (n=23) receive transplacental medication. Monotherapy with β-sympathomimetics, steroid monotherapy, and combination therapy with these agents was given in 11, 5 and 22 cases, respectively. Beta-sympathomimetics improved bradycardia (P<0.001), but no medication could significantly improve the survival rate. Fetal hydrops was associated with a 14-fold increased risk of perinatal death (P=0.001), and myocardial dysfunction was a significant risk factor for poor prognosis (P=0.034). Many adverse effects were observed with steroid treatment, with fetal growth restriction increasing significantly after >10 weeks on steroids (P=0.043).

Conclusions: Treatment with β-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses with and without transplacental medication. It is recommended that steroid use should be limited to <10 weeks to avoid maternal and fetal adverse effects, especially fetal growth restriction and oligohydramnios. (*Circ J* 2012; **76:** 469–476)

Key Words: Anti-Ro/SSA antibody; Congenital atrioventricular block; Pregnancy; Steroids; Transplacental treatment

Fetal congenital bradyarrhythmia is an uncommon but life-threatening disease, especially in the case of complete atrioventricular block (CAVB), which has a poor prognosis because of fetal hydrops, endocardial fibroelastosis and late-onset dilated cardiomyopathy.[1–9] Predominantly untreated CAVB has a significant mortality rate of 14–34%, while congenital CAVB is irreversible and requires a pacemaker in approximately 66% of cases after birth.[10] The association of CAVB with maternal anti-Ro/Sjögren's syndrome A (SSA) antibodies is well established, but the trigger for the maternal antibody interaction with the fetal Ro particle is unknown in some cases of antibody-exposed babies.[2,7–9,11,12]

There is limited evidence for the clinical efficacy of transplacental treatment of congenital AVB.[13–19] Steroids and i.v. immunoglobulins are given as anti-inflammatory treatment, while β-sympathomimetics are used for fetal pacing.[20] A recent

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Table 1. Baseline Characteristics of CAVB Fetuses

	Medication group (n=38)	No medication group (n=23)	P value
Maternal anti-SSA antibodies	29 (76.3)	11 (47.8)	<0.05‡
Gestational age at diagnosis (weeks)	24±3.2	28±5.7	<0.005†
Fetal heart rate at diagnosis (beats/min)	58±7.9	63±14.7	NS†
Fetal hydrops	16 (42.1)	6 (26.1)	NS‡
Fetal myocardial dysfunction	13 (34.2)	7 (30.4)	NS‡
Gestational age at initiation of therapy (weeks)	26±3.6	–	
Fetal heart rate at initiation of therapy (beats/min)	56±8.4	–	
Gestational age at delivery (weeks)	34±4.0	35±4.5	NS†
Birth weight (g)	2,120±620	2,528±653	<0.001†
Delivery mode			
Vaginal	8	7	NS‡
Cesarean section	30	16	NS‡
Permanent pacemaker implantation	14 (46.7)	6 (35.3)	NS‡
Neonatal survival	30 (78.9)	17 (73.9)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.
CAVB, complete atrioventricular block; SSA, Sjögren's syndrome A.

cohort study found an improved survival rate of >90% with initiation of maternal high-dose dexamethasone at the time of CAVB detection, and maintenance of this drug during pregnancy with use of β-sympathomimetics to keep fetal heart rates at >55 beats/min.[9,21] It was also suggested that prolonged use of dexamethasone might render fetuses with congenital CAVB less likely to develop the additional manifestations of myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. Use of steroids, however, is controversial because of the potential risks for the fetus, including problems with neurological development, growth retardation, and oligohydramnios.[22–25]

Few large studies of fetal congenital bradyarrhythmia have been performed in Japan. The aims of the present study were to determine the features of fetal congenital bradyarrhythmia in Japan, and to examine the effects and risks of transplacental treatment for this condition.

Methods

Subjects

Data were collected using questionnaires sent to Departments of Perinatology and Pediatric Cardiology at 750 institutions in Japan over 7 years (2002–2008). The response rate was 60.7% (455 institutions). Fetal bradyarrhythmia was defined as ventricular heart rate <100 beats/min at the time of diagnosis.[4] The following perinatal data were also collected: gestational age at diagnosis and delivery, presence or absence of a congenital heart defect (CHD), type of bradyarrhythmia, method of diagnosis, presence or absence of maternal autoantibodies such as anti-Ro/SSA antibodies, presence or absence of fetal hydrops, presence or absence of fetal myocardial dysfunction, fetal ventricular and atrial heart rate at presentation, prenatal treatment, mode of delivery, and outcome. Adverse effects related to prenatal treatment were also evaluated.

Statistical Analysis

Statistical analysis was performed using STATA 11.1 (StataCorp, College Station, TX, USA) and JMP 9 (SAS Institute, Cary, NC, USA). Data are presented as mean±SD or number of patients and were analyzed using Student's t-test. Categorical variables were evaluated on chi-square test and Fisher's exact test. Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody. Time to fetal or neonatal death was analyzed using the Kaplan-Meier method with a log-rank test and a Cox proportional hazard model. P<0.05 was considered significant.

Results

Baseline Characteristics

A total of 128 cases were registered from 52 institutions during 7 years (2002–2008). All cases of fetal bradyarrhythmia were diagnosed during fetal life using echocardiography. In 8 cases, magnetocardiography was performed due to fetal bradyarrhythmia and family history of long QT syndrome (LQTS). Of the 128 fetuses, 38 (29.7%) had CHD, 15 had left atrial isomerism, 1 had right atrial isomerism, 5 had atrioventricular septal defect, 4 had corrected transposition of the great arteries, 4 had pulmonary stenosis, and 9 had other conditions. Patent ductus arteriosus and atrial septal defect were categorized as an absence of CHD. Ninety fetuses (70.3%) had a structurally normal heart, of whom 61 had CAVB, 16 had second-degree AVB, 8 had sinus bradycardia, 3 had sick sinus syndrome. Nine LQTS cases occurred in combination with another condition.

CAVB

Of the 61 fetuses with a structurally normal heart and CAVB (Table 1), 38 received transplacental medication. No fetus showed improvement of heart block. Monotherapy with β-sympathomimetics was given in 11 cases, steroids were given in 5 cases, and combination therapy with these agents was used in 22 cases. No transplacental medication was given in 23 cases. Ritodrine hydrochloride was used as the β-sympathomimetic agent. Steroids tended to be used in fetuses that were positive for maternal anti-Ro/SSA antibody throughout pregnancy, but the chosen steroid differed among institutions. Maternal i.v. immunoglobulin was not used. After birth, a pacemaker was implanted based on the Japanese guidelines of syncope, ventricular heart rate <50 beats/min, decreased cardiac function, LQTS, and a sudden pause longer than 2–3-fold the regular ventricular heart rate.

Table 2. Factors in Improvement of Bradycardia

	OR	95%CI	P value
β-sympathomimetics	49.02	5.18–464.02	<0.005
Steroids	1.32	0.24–7.20	0.745
β-sympathomimetics+steroids	725,448.8	0	0.996
Fetal heart rate	1	0.93–1.08	0.924
Fetal hydrops	0.41	0.07–2.39	0.319
Fetal myocardial dysfunction	1.14	0.20–6.60	0.883
Maternal anti-Ro/SSA antibodies	0.22	0.04–1.36	0.105

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 3. Factors in Fetal or Neonatal Death

	HR	95%CI	P value
β-sympathomimetics	1.16	0.37–3.63	0.792
Steroids	0.56	0.20–1.58	0.273
Fetal heart rate	0.98	0.92–1.05	0.546
Fetal hydrops	13.84	3.12–61.44	0.001
Fetal myocardial dysfunction	2.44	0.71–8.40	0.157
Maternal anti-Ro/SSA antibodies	1.07	0.33–3.47	0.906

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
HR, hazard ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 4. Factors in Development of Fetal Hydrops

	OR	95%CI	P value
β-sympathomimetics	2	0.35–11.50	0.439
Steroids	0.27	0.04–1.97	0.198
Fetal heart rate	1.01	0.94–1.08	0.813
Fetal myocardial dysfunction	5.71	1.14–28.62	0.034
Maternal anti-Ro/SSA antibodies	0.71	0.13–3.90	0.698

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

The anti-Ro/SSA antibody-positive rate was significantly higher in fetuses treated with transplacental medication compared to those who did not receive this medication (76.3% vs. 47.8%; P=0.031). Gestational age at diagnosis was significantly lower in those receiving transplacental medication (24.0 weeks vs. 28.3 weeks; P=0.003). Fetal ventricular heart rate at diagnosis did not differ between the 2 groups, but the ventricular heart rate was significantly lower in fetuses treated with transplacental medication (56 beats/min vs. 63 beats/min; P=0.034). Birth weight was also significantly lower in fetuses treated with transplacental medication (2,120 g vs. 2,528 g; P=0.006). Gestational age at delivery, neonatal survival rate, and pacemaker implantation rate did not differ between the 2 groups.

Multivariate analysis was performed with adjustment for baseline variables with a known association with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and the presence of maternal anti-Ro/SSA antibodies (Tables 2–4). In this analysis, β-sympathomimetic treatment was significantly associated with improved bradycardia (odds ratio [OR], 49.02; 95% confidence interval [CI]: 5.18–464.02; P<0.001), whereas steroids were ineffective, and no evidence of a synergistic effect was obtained. The presence of maternal anti-Ro/SSA antibodies may inhibit improvement of bradycardia, but this effect was not significant (OR, 0.22; 95%CI: 0.04–1.36; P=0.105). Drug therapy had no significant effect on survival. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies also had no influence on prognosis, but fetal hydrops was associated with a 14-fold increased risk of perinatal death (hazard ratio [HR], 13.84; 95%CI: 3.12–61.44; P=0.001).

Kaplan-Meier survival curves are shown in Figure. The primary endpoint was intrauterine death or neonatal death. Beta-sympathomimetic treatment was not associated with improved prognosis. Steroid also did not improve the prognosis (HR, 0.56; 95%CI: 0.20–1.58; P=0.273). Fetal myocardial dysfunction was a significant risk factor for fetal hydrops (OR, 5.71; 95%CI: 1.14–28.62; P=0.034). Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with fetal hydrops. Beta-sympathomimetic treatment did not inhibit development of fetal hydrops. Steroids tended to inhibit fetal hydrops, but again this effect was not

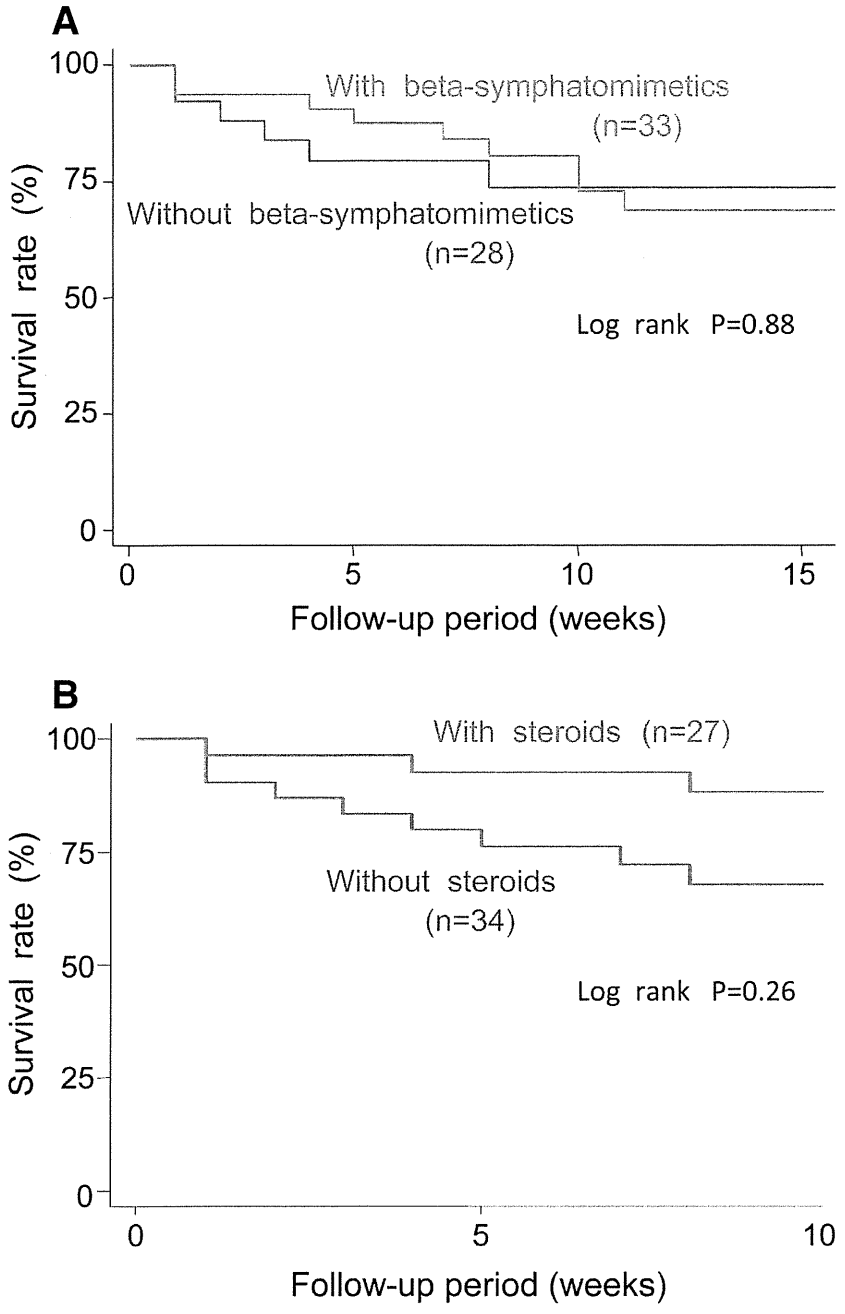

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (A) with and without β-sympathomimetics and (B) with and without steroids. Follow-up period, time from diagnosis in utero to fetal or neonatal death. Significant difference defined as P<0.05.

statistically significant (OR, 0.27; 95%CI: 0.04–1.97; P=0.198). Drug therapy had no significant effect on improvement of fetal myocardial dysfunction.

Second-Degree AVB With Bradycardia

Of the 90 fetuses with a structurally normal heart, second-degree AVB was present in 16 cases (Table 5). Transplacental medication was given in 8 of these cases: β-sympathomimetic monotherapy in 4, steroids in 3, and a combination of these therapies in 1. In the 8 medication cases, fetal ventricular heart rate at diagnosis was significantly lower than that in the non-medication cases (70 beats/min vs. 79 beats/min; P=0.017). No other clinical characteristics differed significantly between the 2 groups. Of the 8 medicated fetuses, 3 developed CAVB, 3 maintained second-degree AVB, 1 improved to first-degree AVB, and 1 had no AVB at the time of delivery. Of the 8 non-medicated fetuses, 2 developed CAVB, 3 maintained second-degree AVB, and 3 had no AVB at the time of delivery. Survival rate did not differ between the groups (87.5%).

Adverse Effects of Transplacental Treatment

Treatment-related adverse events were examined in the 63 fetuses with a structurally normal heart and no fetal hydrops (Table 6). Steroids were given in 23 cases, drugs other than steroids were given in 10 cases, and no treatment was given in 30 cases. Gestational age at delivery did not differ among these 3 groups. In the steroid group, birth weight was significantly lower than in the non-treatment group (2,201 g vs.

Table 5. Second-Degree AVB Fetus Baseline Characteristics vs. Medication

	Medication (n=8)	No medication (n=8)	P value
Maternal anti-Ro/SSA antibodies	4	3	NS‡
Gestational age at diagnosis (weeks)	28±4.3	26±5.0	NS†
Fetal heart rate at diagnosis (beats/min)	70±9.0	79±10.4	<0.05†
Fetal hydrops	2	2	NS‡
Fetal myocardial dysfunction	3	2	NS‡
Gestational age at initiation of therapy (weeks)	29±4.8	–	
Fetal heart rate at initiation of therapy (beats/min)	70±10.0	–	
Gestational age at delivery (weeks)	35±3.8	37±2.1	NS†
Birth weight (g)	2,207±688	2,533±544	NS†
Delivery mode			
Vaginal	2	5	NS‡
Cesarean section	6	3	NS‡
Degree of AVB at delivery			
Complete	3	2	NS‡
Second	3	3	NS‡
First	1	0	NS‡
None	1	3	NS‡
Neonatal survival	7 (87.5)	7 (87.5)	NS‡

Data given as mean±SD or n (%).
P<0.05, significant difference. †Wilcoxon test; ‡chi-square test and Fisher's exact test.
AVB, atrioventricular block; SSA, Sjögren's syndrome A.

Table 6. Baseline Characteristics vs. Treatment Type†

	Steroid treatment (n=23)	Non-steroid treatment (n=10)	No treatment (n=30)
Treatment (weeks)	8.8±4.4	5.6±3.2	–
Gestational age at delivery (weeks)	36±2.6	35.8±2.6	36.8±3.0
Birth weight (g)	2,201±525*	2,413±552	2,713±512*
Fetal arrythmia: CAVB	21	6	23
Fetal arrythmia: Second-degree AVB	1	2	5
Maternal diabetes	1 (4.3)	0	0
Fetal growth restriction	6 (26.1)	0	2 (6.7)
Fetal oligohydramnios	2 (8.7)	0	0
Neonatal adrenal insufficiency	1 (4.3)	0	0

Data given as mean±SD or n (%).
†For fetuses without fetal hydrops and with a structurally normal heart. *P<0.05 (Student's t-test).
CAVB, complete atrioventricular block; AVB, atrioventricular block.

Table 7. Baseline Characteristics vs. Length of Steroid Treatment

	<10 weeks (n=12)	≥10 weeks (n=11)	P value
Treatment (weeks)	5.4±2.7	12.5±2.5	<0.01†
Gestational age at delivery (weeks)	35±3.2	36±1.7	NS†
Birth weight (g)	2,184±569	2,218±503	NS†
Maternal diabetes	0	1 (9.1)	NS‡
Fetal growth restriction	1 (8.3)	5 (45.5)	<0.05‡
Fetal oligohydramnios	0	2 (18.2)	NS‡
Neonatal adrenal insufficiency	0	1 (9.1)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.

2,713 g; P=0.001) and fetal growth restriction was close to being significantly higher than in the non-steroid (26.1% vs. 0%; P=0.050) and non-treatment (26.1% vs. 6.7%; P=0.074) groups. Adverse effects that might have been attributable to the use of steroids included development of oligohydramnios in 8.7% of cases, maternal diabetes in 4.3%, and neonatal adrenal insufficiency in 4.3%. All these adverse effects were observed in cases of steroid use >10 weeks (Table 7). In particular, fetal growth restriction increased significantly after steroid use >10 weeks (45.5% vs. 8.3%; P=0.043).

LQTS

Of the 90 fetuses with a structurally normal heart, 9 (10.0%) were diagnosed with LQTS, including 4 diagnosed on electrocardiography after birth and 5 diagnosed on magnetocardiography during fetal life. The background of the LQTS fetuses included a family history of LQTS (n=2), maternal anti-Ro/SSA antibody (n=2), fetal hydrops (n=3), myocardial dysfunction (n=2), CAVB (n=6), second-degree AVB with bradycardia (n=1), and sinus bradycardia (n=2). In 4 of the 9 cases of LQTS, emergency cesarean section was performed because of fetal ventricular tachycardia/torsades de pointes (VT/TdP) at 33–36 weeks of gestation. In 2 of the 9 cases, fetal hydrops caused neonate death.

Discussion

This is the first large-scale study to investigate the effects and risks of transplacental treatment for fetal congenital bradyarrhythmia in Japan. The results indicate that fetal hydrops is associated with a 14-fold increased risk of perinatal death, and that fetal myocardial dysfunction is a significant risk factor for fetal hydrops. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with neonatal prognosis. Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly with regard to transplacental medication. Maternal and fetal adverse effects were observed in cases of steroid use. In particular, fetal growth restriction increased significantly after steroid use >10 weeks.

Evaluation of Anti-Ro/SSA Antibodies

Ro/SSA is one of the major immunogenic ribonucleoproteins, and antibodies against these proteins are found in a number of connective diseases, especially in Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE). Anti-Ro/SSA antibodies are detected in 60–90% of SS cases and in 30–50% of SLE cases.[26,27] Interestingly, these antibodies are relatively common and are detected in 1–2% of randomly tested pregnant women.[28] Currently, the outcome of anti-Ro/SSA-positive pregnancies is very good when prospectively followed by multidisciplinary teams with experience in this field.[1] Transplacental passage of anti-Ro/SSA antibodies from mother to fetus, however, is associated with a risk of development of neonatal lupus erythematosus (NLE).[2,11,12] NLE is an uncommon but life-threatening disease of the fetus and neonate, with important cardiac complications of CAVB, sinus bradycardia, QTc interval prolongation, endocardial fibroelastosis, and late-onset dilated cardiomyopathy.[3–5] Congenital CAVB develops in 1–5% of anti-Ro/SSA antibody-positive pregnancies, typically between 18 and 24 weeks of gestational age. Predominantly untreated CAVB has a mortality rate of 14–34%,[1–9] consistent with the untreated CAVB mortality rate of 26% in the current study.

The association of NLE with maternal anti-Ro/SSA antibodies is well established, but the trigger of the maternal antibody interaction with the fetal Ro particle is unclear in some antibody-exposed babies. The percentage of maternal anti-Ro/SSA antibody-positive fetuses with CAVB diagnosed in utero is unknown. Brucato et al and Jaeggi et al found maternal anti-Ro/SSA antibodies in 92% of 37 CAVB cases,[7,9] whereas in the present study maternal anti-Ro/SSA antibodies were detected in only 66% of 61 CAVB fetuses with a structurally normal heart. Jaeggi et al also reported that CAVB occurred in 5% of prospectively screened pregnancies with anti-Ro/SSA ELISA levels >100 U/ml, but did not occur in pregnancies with levels <50 U/ml.[6] Approximately two-thirds of anti-Ro/SSA antibody-positive mothers had low anti-Ro/SSA levels and probably little risk of development of fetal cardiac NLE.[8] It is unclear why the anti-Ro/SSA-positive rate in the present study was lower than in other reports. It is unlikely to be due to the sensitivity of the laboratory methods, but it is possible that other undetectable antibodies associated with congenital AVB are present in the Japanese population. Brucato et al and Lopes et al found similar mortality rates in the anti-Ro/SSA-positive and -negative groups,[7,8] and in the present multivariate analysis anti-Ro/SSA antibodies were not associated with prognosis.

Benefits and Risks of Transplacental Treatment

Congenital AVB is a progressively developing disease that evolves through 2 fundamental phases: an early phase characterized by the occurrence of still reversible AV conduction abnormalities (first- or second-degree AVB) and a final phase in which development of irreversible damage of the conduction system leads to the appearance of CAVB.[29] The specific pathogenetic mechanisms involved in the 2 phases have not been clarified, but there are 2 main theories. The first is based on an inflammatory-driven injury elicited by interaction between anti-Ro/SSA antibodies and specific antigens expressed in the conduction tissue of the fetal heart (inflammatory theory). The second theory involves electrophysiologic interference of anti-Ro/SSA antibodies with heart conduction (electrophysiological theory).[20] Consistent with these respective theories, steroids and i.v. immunoglobulins are used for anti-inflammatory treatment, while β-sympathomimetics are given for fetal pacing.

Several studies have found that a ventricular heart rate <55 beats/min is a risk factor for fetal and neonatal death,[4,14] and have recommended transplacental treatment with β-sympathomimetics to increase the heart rate. Jaeggi et al and Maeno et al, however, found that fetuses with CAVB without CHD and with a ventricular heart rate of <55 beats/min were not at risk.[30,31] In the present study, fetal ventricular heart rate did not influence fetal hydrops and prognosis, but treatment with a β-sympathomimetic agent was significantly associated with improved bradycardia.

To date, evidence of clinical efficacy of transplacental treatment has been limited to cases of congenital AVB.[13–19] Jaeggi et al reported a significant improvement in the outcome of fetal CAVB simultaneously with the introduction of routine perinatal treatment guidelines in 1997.[9] Hutter et al obtained an improved survival rate of >90% by initiation of maternal high-dose dexamethasone at the time of CAVB detection and maintenance of this dose during pregnancy, with addition of β-sympathomimetics to keep the fetal heart rate above 55 beats/min.[21] It was also suggested that prolonged use of dexamethasone might render a fetus with congenital CAVB less likely to develop additional manifestations of cardiac NLE such as myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. The present findings suggest that use of steroids might render the affected fetus less likely to develop fetal hydrops, but that the neonatal survival rate improved only to 79%. The reason for the relatively bad prognosis in the present study may have been the difference in the rate of fetal hydrops compared to the Hutter et al study (42% vs. 10%). Undetectable autoantibodies or virus infection may be related to the increased rate of fetal hydrops in the Japanese population. Furthermore, Hutter et al initiated maternal high-dose dexamethasone at the time of CAVB diagnosis, at a mean gestational age of 24 weeks. The mean age of diagnosis was similar in the present study, but mean gestational age at which steroids were started was 26 weeks. In addition, the percentage of steroids used in transplacental treatment was

lower in the present patients (71% vs. 95%). These findings suggest that sufficient steroid dose at an early stage is very important to prevent fetal hydrops and to improve prognosis.

Use of steroids is controversial because of the potential risks for the fetus and mother, including problems with fetal growth restriction, oligohydramnios, and neurological development. Animal models suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain, and human studies suggest that antenatal and postnatal dexamethasone may negatively affect a child's neuropsychological development.[22–24] In contrast, Brucato et al found no negative effects on neuropsychological development and intelligence in a cohort of preschool- and school-age children with CAVB who had been prenatally exposed to maternal anti-Ro antibodies and prolonged dexamethasone treatment.[25] The association of fetal growth restriction and oligohydramnios with antenatal steroids is well established, but the amount and length of steroid treatment that can be used safely is unclear. We note that development of fetal growth restriction and oligohydramnios are dose-related complications of steroids. Consequently, we recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects.

Prevention of Progression to Congenital CAVB

There are many case reports describing prevention of congenital CAVB, and first- or second-degree AVB is also relatively common and often normalizes spontaneously before or soon after delivery.[32] Recent prospective studies suggest that steroids and i.v. immunoglobulins are not beneficial for preventing progression to congenital AVB.[33,34] Similarly, the present study found a lack of superiority of transplacental treatment for second-degree AVB with bradyarrhythmia.

LQTS

Recent evidence has shown that anti-Ro/SSA antibodies are associated with prolongation of the QTc interval.[35] Although the exact arrhythmogenic mechanisms have not been clarified, anti-Ro/SSA antibodies may trigger rhythm disturbances through inhibition of cross-reactions with several cardiac ionic channels, including calcium channels and the hERG potassium channel.[36,37] Beta-sympathomimetics may trigger life-threatening arrhythmia such as VT/TdP in patients with LQTS, and therefore use of these drugs should be avoided in fetuses with QTc interval prolongation.[38,39] In the present study, in 4 of the 9 LQTS cases, emergency cesarean section was performed because of fetal VT/TdP at 33–36 weeks of gestational age. Oka et al also recently described atrioventricular block-induced TdP.[40] With this background, we recommend avoidance of β-sympathomimetics in a fetus with a heart rate >55 beats/min. Furthermore, assessment of QTc interval prolongation on magnetocardiography may be required to evaluate the risk of fetal congenital bradyarrhythmia.

Study Limitations

There were several limitations in the present study due to retrospective data selection bias and the relatively small sample size. The nature of a multicenter retrospective observational study using a questionnaire is such that the clinical data obtained vary among cases, so treatment bias may exist. Only ritodrine hydrochloride was used as β-sympathomimetic treatment, but was given in cases involving fetal heart rate >55 beats/min at some institutions, while dexamethasone, betamethasone and prednisolone were used as steroids at different doses among institutions. The follow-up period after birth was insufficient to permit analysis of long-term morbidity and mortality, and this prevented evaluation of potential long-term benefits and risks of transplacental medication. Finally, the sample size might have been too small to detect the effects of steroids on fetal congenital bradyarrhythmia. The steroid effect may become significant in a study with a higher number of cases.

Guidelines are required for transplacental treatment of fetal congenital bradyarrhythmia and follow-up after birth. We expect to analyze long-term outcome of fetal congenital bradyarrhythmia in a future study. Further large prospective studies are also needed to establish the most appropriate treatment strategies in Japan.

Conclusion

Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses treated with and without transplacental medication. We recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects, with fetal growth restriction and oligohydramnios being of particular concern.

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Disclosures

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Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome

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BACKGROUND Men and women with type 1 long QT syndrome (LQT1) exhibit time-dependent differences in the risk for cardiac events.

OBJECTIVE We hypothesized that sex-specific risk for LQT1 is related to the location and function of the disease-causing mutation in the *KCNQ1* gene.

METHODS The risk for life-threatening cardiac events (comprising aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) from birth through age 40 years was assessed among 1051 individuals with LQT1 (450 men and 601 women) by the location and function of the LQT1-causing mutation (prespecified as mutations in the intracellular domains linking the membrane-spanning segments [ie, S2–S3 and S4–S5 cytoplasmic loops] involved in adrenergic channel regulation vs other mutations).

RESULTS Multivariate analysis showed that during childhood (age group: 0–13 years) men had >2-fold ($P < .003$) increased risk for ACA/SCD than did women, whereas after the onset of adolescence the risk for ACA/SCD was similar between men and women (hazard ratio = 0.89 [$P = .64$]). The presence of cytoplasmic-loop mutations was associated with a 2.7-fold ($P < .001$) increased risk for ACA/SCD among women, but it did not affect the risk among men (hazard ratio 1.37; $P = .26$). Time-dependent syncope was associated with a more pronounced risk-increase among men than among women (hazard ratio 4.73 [$P < .001$] and 2.43 [$P = .02$], respectively), whereas a prolonged corrected QT interval (≥500 ms) was associated with a higher risk among women than among men.

CONCLUSION: Our findings suggest that the combined assessment of clinical and mutation location/functional data can be used to identify sex-specific risk factors for life-threatening events for patients with LQT1.

KEYWORDS: Cytoplasmic-loop mutations; Sex; Long QT syndrome; Sudden cardiac death

ABBREVIATIONS **ACA** = aborted cardiac arrest; **C-loop mutations** = cytoplasmic-loop mutations; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LQTS** = long QT syndrome; **LQT1** = long QT syndrome type 1; **MS** = membrane spanning; **QTc** = corrected QT interval; **SCD** = sudden cardiac death

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Introduction

Long QT syndrome type 1 (LQT1) is the most commonly occurring of the congenital long QT syndromes (LQTS).[1] It is caused by mutations in the *KCNQ1* gene that impair the slow-acting potassium channel that gives rise to slow delayed rectifier potassium current (I_{Ks}). The resulting prolongation of ventricular repolarization increases the potential for cardiac arrhythmogenic events that can cause syncope or sudden cardiac death (SCD). Patients with LQT1 experience the majority of their events during exercise, possibly because the phase 3 I_{Ks} repolarizing current activates during increased heart rate and is essential for QT-interval adaptation during tachycardia.[1,2] Prior studies have shown that mutations located at the membrane-spanning (MS) region and missense vs nonmissense mutations are associated with a greater risk for cardiac events in patients with LQT1.[3] The MS region includes the MS domains and the MS linkers. Mutations in the intracellular linkers that connect the MS domains of the KCNQ1 (Kv7.1) channel subunit (defined herein as the S2–S3 and S4–S5 cytoplasmic [C]-loop mutations) were shown to affect adrenergic channel regulation by protein kinase A[4] and may therefore predispose to increased risk for life-threatening events in this population.[5]

The phenotypic expression of LQT1 is affected by sex and age, wherein men with LQT1 experience increased risk for cardiac events, mainly during the childhood period.[6] Prior studies, however, did not relate sex-specific risk in this population to the location and function of the disease-causing mutation in the *KCNQ1* gene. Furthermore, sex differences in the clinical course of LQT1 were related previously to a cardiac event composite end point, which comprised mostly nonfatal syncope. Accordingly, the present study was designed to evaluate whether the combined assessment of clinical and mutation location/functional data can identify sex-specific risk factors for life-threatening cardiac events in men and women with LQT1.

Methods

Study population

The study population comprised 1051 LQT1-positive subjects from 259 proband identified families. Patients were drawn from the Rochester, NY, enrolling center (center 1) of the International LQTS Registry (n = 755), the Netherlands LQTS Registry (n = 85), and the Japanese LQTS Registry (n = 83), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project: Denmark (n = 43), Israel (n = 34), Sweden (n = 4), and Salt Lake City, UT (n = 47). The proband in each family had otherwise unexplained, diagnostic corrected QT-interval (QTc) prolongation or experienced LQTS-related symptoms. Patients with congenital deafness were excluded from the study.

Data collection and management

For each patient, information on personal history, including cardiac events, electrocardiograms, and therapies, as well as family history was obtained at enrollment. Clinical data were then collected yearly on prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiogram findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter defibrillator (ICD), and the occurrence of LQT1-related cardiac events. The QT interval was corrected for heart rate (QTc) by using Bazett's formula.[7] Data common to all LQTS registries involving genetically tested individuals were merged electronically into a common database for the present study.

Genotype characterization

The *KCNQ1* mutations were identified with the use of standard genetic tests conducted in academic molecular genetic laboratories including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN; Boston Children's Hospital, Boston, MA; Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands; and Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Mutations were defined as any nonsynonym rare variants (<1% of the healthy population) identified in a proband with a prolonged QT interval. Based on prior data regarding mutation location/function and arrhythmic risk in LQT1,[3–5,8] mutations were categorized by their location and type in the *KCNQ1*-encoded channel subunit as follows: (1) missense mutations in the MS region: defined as amino acid residues from 120 to 355, excluding mutations within the MS linkers; (2) missense mutations in the C loops: defined as the coding sequence involving amino acid residues from 174 to 190 (S2–S3 linker) and from 242 to 259 (S4–S5 linker); (3) missense mutations in the N-terminus region, defined as amino acid residues before 120, and the C-terminus region, defined as amino acid residues after residue 355, were combined into one category labeled as the other region for this analysis (hence called the N/C terminus); and (4) other LQT1 mutations as the reference group (ie, splice sites, in-frame insertions, in-frame deletions, nonsense, and frameshift).

The specific mutations included in the present study, by location, type, and number of patients, are detailed in the Supplementary Appendix Table 1, and the distribution of the mutations in the *KCNQ1* gene by their frequency among study 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 aborted cardiac arrest (ACA) (requiring defibrillation as part of resuscitation), or LQT1-related SCD (abrupt in onset without

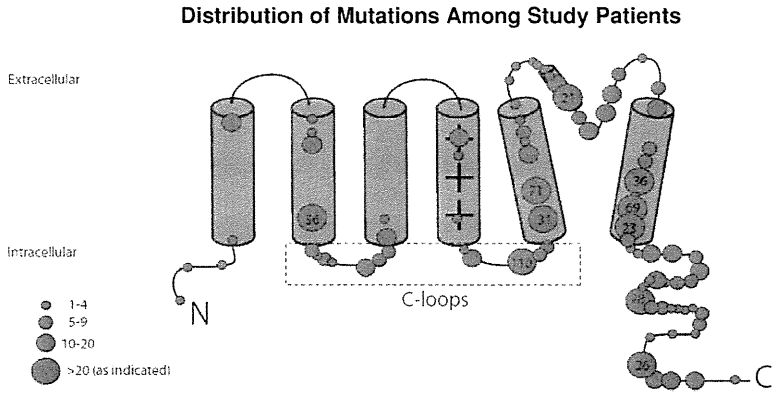

Figure 1 Distribution of mutations in the *KCNQ1* (Kv7.1) potassium channel subunit among study patients. Numbers in larger circles denote the number of patients with the mutation. C loops = cytoplasmic loops.

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 by using the chi-square test for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables. The cumulative probability of a first ACA or SCD by sex and by mutation location was assessed by using the Kaplan-Meier method, and significance was tested by using the log-rank test. Follow-up was censored at age 40 years 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 sex, QTc duration (categorized as a 3-level covariate: >500 ms, 500–550 ms, <500 ms [reference]), mutation location and type (as defined above), the occurrence of syncope during follow-up, and medical therapy with beta-blockers. Syncope and beta-blocker therapy were assessed as time-dependent covariates in the multivariate models. To avoid violation of the proportional hazards assumption due to sex-risk crossover during adolescence, we employed an age-sex interaction term in the total population multivariate model. The effect of each covariate in men and women was assessed by interaction-term analysis (ie, by including a sex-by-risk factor interaction term in the multivariate models), with interactions tested one at a time. Patients without available baseline QTc data (n = 151) were included as a separate (QTc missing) covariate in the multivariate models.

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.[9] 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, NC). A 2-sided .05 significance level was used for hypothesis testing.

Results

The clinical characteristics of the study patients by sex are shown in Table 1. Baseline QTc was similar between men and women during childhood and significantly higher among women after the onset of adolescence. During follow-up, similar numbers of men and women were treated with beta-blockers, but a higher proportion of women were treated with an ICD. There were no significant sex differences in the distribution of the mutation by location (Table 1). However, patients with missense mutations localizing to the C loops exhibited a significantly longer baseline QTc (503 ± 58 ms) than did patients with other mutations (480 ± 51 ms; $P <$ .001).

Risk factors for ACA or SCD in the total LQT1 population

During follow-up, 138 study patients (13%) experienced the primary end point of a first ACA or SCD. Kaplan-Meier event rates were significantly higher among men than among women throughout follow-up (P = .008 for the overall difference; Figure 2). Notably, life-threatening cardiac events among men occurred predominantly during childhood, whereas among women event rates increased after this time period. Thus, by age 14 years, the cumulative probability of ACA or SCD was 10% among men as compared with only 3% among women, and by age 40 years, the respective events rates were 19% and 15% (Figure 2).

Consistent with those findings, multivariate analysis in the total study population showed that during childhood men had >2-fold (P = .003) increase in the risk for ACA or SCD as compared with women whereas after the onset of adolescence, there was no statistically significant difference in the risk for ACA or SCD between men and women (hazard ratio [HR] 0.89; P = .64; Table 2). Additional risk

Table 1 Characteristics of the study population

Characteristic	Men (n = 450)	Women (n = 601)	P
ECG parameters			
Overall QTc (ms)	473 ± 55	486 ± 55	<.001
Age ≤ 13 y	486 ± 53	485 ± 54	.21
Age > 13 y	460 ± 53	487 ± 56	<.001
QTc > 500 ms (%)	22	27	.09
RR (ms)	842 ± 220	837 ± 199	.55
Mutation location (%)			
Cytoplasmic loop (S2–S3 or S4–S5 linkers)	19	19	.92
MS	53	54	.67
N/C terminus	28	26	.58
Mutation type (%)			
Missense	83	79	.13
LQTS therapies during follow-up (%)			
Beta-blockers	45	46	.74
Pacemaker	1.6	1.5	.94
ICD	4	9	.003
LCSD	1.1	0.5	.30
Cardiac events during follow-up (%)			
Syncope	35	36	.84
ACA	3	4	.22
SCD	13	8	.007
Appropriate ICD shocks	0.2	1.7	.03
ACA or SCD*	15	11	.07

Values are mean ± SD unless otherwise indicated.

ACA = aborted cardiac arrest; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LCSD = left cervical sympathetic denervation; LQTS = long QT syndrome; MS = membrane spanning; QTc = corrected QT interval; SCD = sudden cardiac death; SD = standard deviation.

*Only the first event for each patient was considered.

factors within the total study population included the presence of missense mutations localizing to the C loops (1.9-fold risk increase [$P = .005$]), QTc 500–550 and >550 ms (>3-fold and >4-fold risk increase, respectively [$P < .001$ for both]), and the occurrence of syncope during follow-up (3.4-fold risk increase [$P < .001$]; Table 2). Results were similar when the secondary end point of a first ACA, SCD, or appropriate ICD shock was assessed.

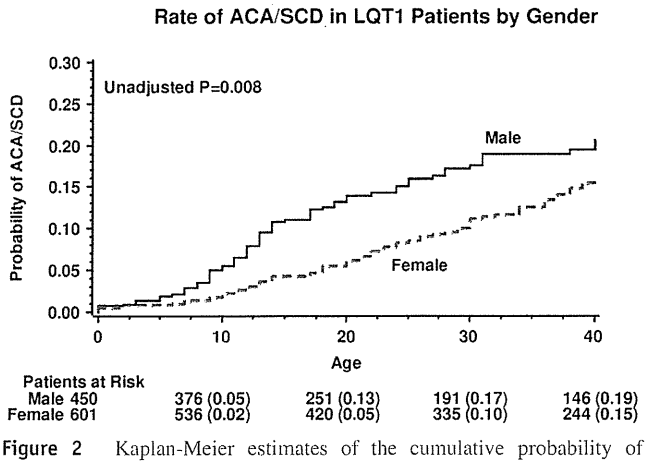

Figure 2 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in patients with LQT1 by sex. ACA = aborted cardiac arrest; LQT1 = long QT syndrome type 1; SCD = sudden cardiac death.

Table 2 Multivariate analysis: Risk factors for ACA/SCD among all patients with LQT1*

Risk factor	Relative risk: Hazard ratio	95% Confidence interval	P
Sex			
Men vs women ≤ 13 y	2.31	1.41–3.92	.003
Men vs women >13 y	0.92	0.61–1.51	.72
Mutation location (vs nonmissense mutations)			
Cytoplasmic loop (S2–S3/S4–S5 linkers)	1.93	1.37–2.75	.005
MS (S1, S2, S3, S4, S5, P-loop, S6)	1.02	0.71–1.85	.51
N/C terminus	0.96	0.52–1.57	.72
QTc duration (ms)			
>550 vs <500	4.18	2.06–8.46	<.001
500–550 vs <500	3.35	1.83–6.11	<.001
Time-dependent syncope			
Syncope vs no syncope	3.40	2.22–5.21	<.001

ACA = aborted cardiac arrest; LQT1 = long QT syndrome type 1; MS = membrane spanning; QTc = corrected QT interval; SCD = sudden cardiac death.

*Models were further adjusted for missing QTc values, time-dependent beta-blocker therapy.

Sex-specific risk factors for life-threatening cardiac events in patients with LQT1

Kaplan-Meier survival analysis showed that women with LQT1 with missense C-loop mutations exhibited a significantly higher rate of ACA or SCD than did women whose LQT1-causative mutation localized elsewhere ($P < .001$ for the overall difference during follow-up; Figure 3A). In contrast, among men, the respective rates of ACA or SCD remained high, predominantly during the childhood period, regardless of mutation location/type ($P = .33$ for the overall difference during follow-up [Figure 3B]).

Sex-specific multivariate analysis (Table 3) showed that women with C-loop mutations exhibited nearly a 3-fold ($P = .01$) increased risk for ACA or SCD than did women with other mutation types, whereas the risk for ACA or SCD among men was not significantly different by mutation location/type (P value for mutation-location-by-sex interaction = .07). Similar results were observed in an additional analysis in which the large subset of patients with the V254M C-loop mutation was excluded from the multivariate models (risk associated with C loop vs other mutations among women: HR 2.55, 95% confidence interval [CI] 1.02–5.94; among men: HR 1.03, 95% CI 0.33–4.11).

Additional risk factors for ACA or SCD among both men and women included a prolonged QTc and the occurrence of

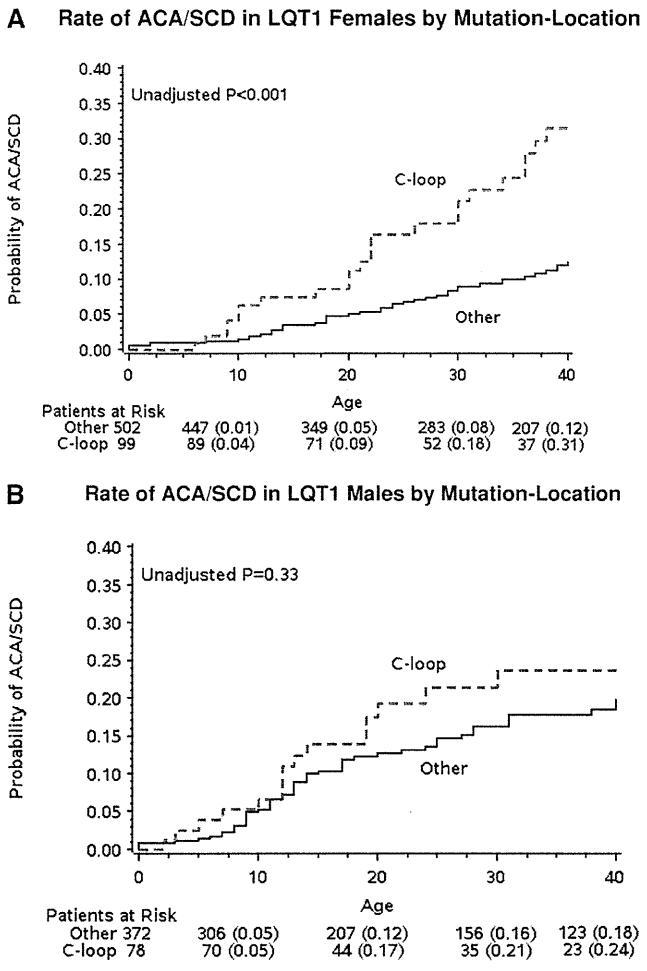

Figure 3 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in (**A**) women with LQT1 and (**B**) men with LQT1, by mutation location. ACA = aborted cardiac arrest; C-loop mutations = cytoplasmic-loop mutations; LQT1 = long QT syndrome type 1; SCD = sudden cardiac death.

time-dependent syncope (Table 3). Notably, women with prolonged QTc, both in the range of 500–550 ms and >550 ms, experienced a pronounced increase (approximately 6-fold) in the risk of ACA or SCD, whereas the risk associated with a prolonged QTc in men was more modest and evident only in those with QTc >550 ms (Table 3 and Figures 4A and B, respectively). The occurrence of syncope during follow-up was associated with a 4-fold ($P < .001$) increase in the risk for subsequent ACA or SCD among men and with a 2.4-fold ($P = .002$) increase in the risk for subsequent ACA or SCD among women.

The combined assessment of clinical and genetic data identified a very low rate of life-threatening events (0.03 events per 100 patient-years) among women aged 13 years or younger without C-loop mutations, no history of prior syncope, and QTc <500 ms.

Time-dependent medical therapy with beta-blockers was associated with a significant 61% reduction in the risk for ACA or SCD in the total study population (HR 0.39; 95% CI 0.22–0.70; $P = .001$), with beta-blocker protection seen similarly between men and women (P values for beta-blocker-by-sex interaction = .56). Notably, this analysis showed that the risk associated with C-loop mutations in women was even more pronounced among those who did not receive beta-blocker therapy (HR 4.51; 95% CI 2.57–7.23; $P < .001$).

Discussion

In the present study, we assessed for the first time sex-specific risk factors for life-threatening cardiac events in a large population of 1051 genetically confirmed patients with LQT1. Our findings show that among probands and relatives with LQT1, (1) men exhibit a significantly higher rate of life-threatening cardiac events than do women, especially prior to puberty, and (2) mutation location shows a sex-specific association with the risk for ACA or SCD. Thus, the risk for life-threatening events was shown to be increased among women with LQT1 with mutations localizing to C-loop domains (S2–S3 and S4–S5) of the *KCNQ1*-encoded protein, whereas the risk for ACA or SCD among men with LQT1 was high even among those who harbored mutations localizing to other regions of the channel that had been ascribed previously as lower-risk mutations. These findings suggest that a combined approach that incorporates clinical and genetic data can be used for improved risk assessment and management of men and women with LQT1.

A previous study from the International LQTS Registry has shown that men with LQT1 have an increase in the risk for any LQT1-related cardiac event, including syncope, during childhood, whereas after the onset of adolescence the risk for events in this population is attenuated without a significant sex difference.[6] Because of a limited sample of 243 patients with LQT1, the study did not assess sex-related differences in the risk for only life-threatening cardiac events (ACA or SCD) in this population. Thus, our findings of the present study extend prior observations and show that men with LQT1 display a higher rate of ACA or SCD than do women from birth through age 40 years, with a predominant risk increase during the childhood period.

Patients with LQT1 experience ventricular tachyarrhythmias more frequently during physical effort,[2] possibly due to the lack of adaptive QT shortening with decreasing RR intervals during tachycardia.[10] Thus, the early predominance of life-threatening cardiac events among men may be related to sex differences in the level of physical activity during childhood among registry patients. After the onset of adolescence, an increase in the levels of testosterone, which was shown to shorten action potential duration and ventricular repolarization,[11–13] may result in a reduction in the risk for arrhythmic events in men. This mechanism is supported by the fact that the risk for life-threatening events during childhood was higher among men despite the fact that the average QTc was similar between men and women during this time period, whereas after the onset of adolescence the QTc was significantly reduced in men and remained virtually unchanged in women (Table 1).

Table 3 Multivariate analysis: Risk factors for ACA/SCD among patients with LQT1 by sex*†

	Men with LQT1		Women with LQT1	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Mutation location (vs nonmissense mutations)				
Cytoplasmic loop (S2–S3/S4–S5 linkers)	1.21 (0.72–2.04	0.48	2.62 (1.59–4.26)	<.001
MS	1.02 (0.63–1.97)	0.54	1.01 (0.62–1.89)	.56
N/C terminus	0.89 (0.52–1.91)	0.87	1.14 (0.51–2.37)	.43
QTc duration (ms)				
500–550 vs <500	1.70 (0.63–4.57)	0.29	6.85 (2.74–17.10)	<.001
>550 vs < 500	3.11 (1.19–8.15)	0.02	5.93 (1.89–18.62)	.002
Time-dependent syncope				
Syncope vs no syncope	4.06 (2.22–7.41)	<0.001	2.43 (1.43–4.85)	.002

ACA = aborted cardiac arrest; CI = confidence interval; HR = hazard ratio; LQT1 = long QT syndrome type 1; QTc = corrected QT interval; SCD = sudden cardiac death; MS = membrane spanning.

*Findings were further adjusted for missing QTc values, time-dependent beta-blocker therapy.

†Models were carried out in the total population by using interaction-term analysis, with interactions tested one at a time; cytoplasmic loop-by-sex interaction = .07; all other interaction *P* values were >.10.

Mutations located in the MS region, including the MS domains and the C loops, of the KCNQ1 protein have been associated with greater prolongation in the QTc during exercise[14] and an increase in the risk for cardiac events in patients with LQT1.[3] Importantly, the C loops were shown to modify the function of KCNQ1 channel subunit, including functional interaction with the auxiliary beta subunits encoded by KCNE1 and modulation of the channel's protein kinase A (PKA)-dependent, adrenergic regulation.[4] Thus, patients who harbor C-loop mutations may be sensitive to even mild degrees of adrenergic stimulation, resulting in arrhythmic events that may occur during less intense physical activity. This mechanism may explain the sex-specific association of mutation location to arrhythmic risk shown in the present study, as women who carry mutations in the adrenergic-sensitive C loops may have an increased risk for life-threatening events even during milder degrees of physical activity. In contrast, participation in more intense physical activity among men with LQT1, especially during childhood, may predispose them to arrhythmic events even among those who carry non–C-loop mutations (which are less sensitive to sympathetic activation). It is also possible that sex differences in the regulation of the ion channel contribute to the differential effect of mutation location/function on arrhythmic risk between men and women.

Similar to prior studies,[15–17] we have also shown that QTc is a major risk factor for cardiac events in patients with LQTS. However, our data suggest that in LQT1 the risk associated with QTc is more pronounced among women (who exhibited >6-fold risk with QTc exceeding 500 ms, whereas a significant risk increase among men was evident only among those with QTc >550 ms).

It was suggested recently that patients with LQT1 experience a very low rate of cardiac events during beta-blocker therapy.[18] In the present study, medical therapy with beta-blockers was associated with a pronounced reduction in the risk for ACA or SCD in the total LQT1 population, without a statistically significant difference between men and women. However, our findings suggest that sex-specific risk factors should be taken into account in the management of patients with LQT1. These clinical and mutation-related risk factors are shown in Figure 1 of the Supplementary Appendix and include (1) the preadolescence period in men, especially among those who experience syncope during childhood and those with QTc >550 ms, and (2) following the onset of adolescence in women, especially among those with C-loop mutations, QTc ≥500 ms, and/or history of syncope.

Study limitations

Although we have shown recently that the S2–S3 and S4–S5 C-loop linkers have an important functional role in adrenergic channel regulation through PKA,[4,5] further studies are needed to relate the functional expression of discrete *KCNQ1* mutations to sex-specific risk in LQT1, and their interaction with possible hormonal modulation of cardiac risk in this population.

The present study shows that beta-blocker therapy is associated with a significant reduction in the risk for life-threatening events in both men and women with LQT1. However, because of sample size limitations, we did not evaluate sex-specific differences in response to beta-blocker therapy between patients with LQT1 with higher-risk (and adrenergic-sensitive) C-loop mutations and those with mutations localizing elsewhere. In addition, we did not carry out comprehensive analysis of the relationship between all functional regions of the *KCNQ1*-encoded protein (including functional areas within the C-terminus or N-terminus domains) and sex-specific risk.

We excluded patients with congenital deafness from the study. However, 12 patients (1%) had 2 different mutations in the *KCNQ1* gene. To validate the consistency of the results for patients with single mutations, all multivariate models were repeated after excluding the 12 patients with >1 mutation. This confirmatory analysis yielded virtually identical results regarding the risk associated with clinical factors and mutation location as in the primary analysis.