Table 2 SQTS Diagnostic Criteria: Modified Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

Abbreviations as in Table 1.

leads in the inferior leads (II, III, aVF), lateral leads (I, aVL, V_4 to V_6), anterior leads (V_1 to V_3), or combinations thereof. The contour of the ST segment was classified as having either upsloping or horizontal (downsloping) morphological features. Patients with ICD were assessed for implant indication, delivered therapies, and device complications. We elected to explore the risk-stratifying value of specific variables within the Gollob scoring system. Thus, the diagnostic Gollob score was modified, by excluding clinical events, into a new prognostic score referred to as the modified Gollob score (Table 2).

Statistical analysis. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]: 25th to 75th percentile). Analyzed continuous variables are presented only as medians with IQR and were analyzed using the Wilcoxon rank sum test. Categorical variables are presented as counts with percentages and were analyzed using the Fisher exact test or the chi-square test. Correlation between continuous data was analyzed using the Spearman correlation coefficient. Two-tailed p values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Clinical data. There were 25 patients and a total of 21 (84%) were male. Their clinical data are presented in Table 3. Patients were followed up for a median of 5.9 years (IQR: 4 to 7.1 years). Patient age at the time of clinical presentation ranged from 1 day to 21 years (13.4 ± 6 years, median: 15 years, IQR: 9 to 18 years), with 9 patients (36%) younger than 12 years.

ECG. The QT interval varied from 160 to 360 ms (279 ± 51 ms, median: 290 ms, IQR: 280 to 300 ms), whereas the QTc interval ranged from 194 to 355 ms (304 ± 41 ms, median: 312 ms, IQR: 286 to 335 ms). The J point-to-T peak interval ranged from 63 to 180 ms (132 ± 35 ms, median: 140 ms, IQR: 119 to 160 ms). Arrhythmias were common: 4 patients had atrial fibrillation, 6 had VF, and 1 had supraventricular tachycardia (SVT) at presentation.

GENETIC TESTING. Genetic testing was undertaken in 21 of the 25 patients, and 5 patients had a confirmed mutation. All gene-positive patients were symptomatic, including a 3-month-old young female with recurrent atrial fibrillation since the age of 4 days and associated sinus and atrioventricular node dysfunction (KCNQ1 V141M). Tables 3 and 4 outline the culprit genes, specific mutations, and associated symptoms and arrhythmias detected in the gene-positive cohort.

FAMILY HISTORY. A personal or familial history of cardiac arrest was present in 16 (84%) of 25 patients. A familial history of SCD, presumed to be arrhythmogenic, was present in 5 symptomatic patients and in 6 asymptomatic patients. These involved 6 siblings (4 young males and 2 young females), 2 uncles, and 1 father. The equal distribution of familial SCD among symptomatic and asymptomatic individuals suggests that SCD alone may not predict prognosis, although numbers were relatively small in this study. Among the entire cohort, there was a positive family history for a clinical diagnosis of SQTS in 17 (68%) patients, equally distributed between parents and siblings. Among the patients with atrial fibrillation, only 1 of 4 had a family history of atrial fibrillation. In the patients with VF, only 1 of 6 had a first-degree relative (father) with SCD. Overall, the prevalence of symptomatic family members did not seem to be more common in symptomatic patients, although a much larger cohort would be required to assess confidently whether a symptomatic family member predicts individual risk. Only 4 of 25 patients had no family history of SQTS or SCD.

Symptomatic versus asymptomatic patients. Of the entire cohort, 14 (56%) patients had 1 or more clinical features associated with SQTS, including aborted SCD in 6 (24%), unheralded syncope in 4 (16%), and palpitations with documented atrial fibrillation in 4 (16%). The remaining 11 (44%) patients were asymptomatic, 10 of whom were identified through family screening and the remaining through an incidental ECG finding of a very short QTc interval (292 ms). There was no significant difference in median age between symptomatic and asymptomatic patients (median: 15 years, IQR: 8 to 17 years vs. median: 17 years, IQR: 9 to 18 years, $p = 0.621$). All but 1 of the asymptomatic cases had a family history of SQTS or unexplained SCD.

ECG PARAMETERS. No differences were found in the ECG parameters between asymptomatic and symptomatic patients (Table 3). Although the QTc interval tended to be shorter in symptomatic patients (median: 306 vs. 330 ms), the difference was not statistically significant ($p = 0.207$).

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Table 3 Characteristics of All Patients

Variable	Total (n = 25)	Symptomatic* (n = 14)	Asymptomatic (n = 11)	p Value
Patient age at presentation (yrs)	15 (9–18)	15 (8–17)	17 (9–18)	0.621
Age <12 yrs	9 (36%)	4 (28.6%)	5 (45.5%)	0.434
Male	21 (84%)	11 (78.6%)	10 (90.9%)	0.604
Follow-up duration (yrs)	5.9 (4.4–7.1)	5.7 (4.8–7.4)	6.1 (3.2–6.9)	0.460
Symptoms				
Aborted SCD	6 (24%)	6 (43%)	—	
Unheralded syncope	4 (16%)	4 (28.5%)	—	
Palpitations†	4 (16%)	4 (28.5%)	—	
Modified Gollob score	5 (4–5)	5 (4–6)	4 (4–5)	0.044
Genetic mutation				
KCNH2	2 (8%)	2 (14%)	0	
KCNJ2	2 (8%)	2 (14%)	0	
KCNQ1	1 (4%)	1 (7%)	0	
ECG parameters				
QT (ms)	290 (280–300)	280 (200–300)	295 (280–320)	0.333
QTc (ms)	312 (286–335)	306 (252–329)	330 (292–335)	0.207
J point-to-T peak interval (ms)	140 (119–160)	130 (80–160)	140 (120–160)	0.344
J point-to-T peak interval <120 (ms)	7 (28%)	6 (42.9%)	1 (9.1%)	0.090
Early repolarization	12/24 (50%)	6/14 (43%)	6/10 (60%)	0.680
Family history				0.620
SQTS	8 (32%)	4 (28.6%)	4 (36.4%)	
SCD	4 (16%)	3 (21.4%)	1 (9.1%)	
SCD and SQTS	9 (36%)	4 (28.6%)	5 (45.5%)	
Negative	4 (16%)	3 (21.4%)	1 (9.1%)	
ICD	11 (44%)	8 (57.1%)	3 (27.3%)	0.227
Appropriate shocks	2 (18%)	2 (25%)	0	
Inappropriate shock	7 (63.6%)	4 (50%)	3 (100%)	
Complications‡	9 (81.8%)	6 (75%)	3 (100%)	

Values are median (interquartile range) or n (%). *Only patients with aborted sudden cardiac death, syncope, or documented ventricular or atrial fibrillation at presentation or during follow-up were considered symptomatic for short QT syndrome. †Palpitations and atrial fibrillation or supraventricular tachycardia. ‡Including inappropriate shocks.

ECG = electrocardiography; ICD = implanted cardiac defibrillator; J point-to-T peak interval = interval in milliseconds measured on standard electrocardiography ECG from the J-point to the peak T-wave voltage; SCD = sudden cardiac death. Other abbreviations as in Table 1.

There was a trend toward a higher prevalence of short J point-to-T peak interval (<120 ms) in the symptomatic versus the asymptomatic patients (42.9% vs. 9.1%, p = 0.090). Only 1 of the asymptomatic patients had a short J point-to-T peak interval. The presence of early repolarization did not differ between symptomatic and asymptomatic patients. Early repolarization was found in the anterior (n = 2), anterolateral (n = 2), lateral (n = 1), and anteroinferolateral (n = 1) leads in 43% of symptomatic cases. In 60% of asymptomatic cases, early repolarization was found in the inferolateral (n = 3) cases and in the anterior or lateral leads, or both (n = 3). In all cases, early repolarization had an upsloping ST segment pattern (Fig. 1).

GOLLOB DIAGNOSTIC SCORE FOR SQTS. Asymptomatic patients had Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher Gollob scores ranging from 4 to 10 (median: 6, IQR, 6 to 8, p < 0.001).

A modified Gollob score, excluding clinical events, was assigned to each patient. Asymptomatic patients had modified Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher scores ranging from 3 to 8 (median: 5, IQR: 4 to 6, p = 0.044).

ABORTED SCD. Aborted SCD occurred in 6 (24%) of 25 patients. These patients had a longer follow-up duration

Table 4 Genetic Mutations in the Pediatric Cohort

Age (yrs)	Sex	Gene	Mutation	Current	Symptoms	Arrhythmias
3	F	KCNQ1	V141M	IKs	None	Atrial fibrillation, sinus, and atrioventricular node dysfunction
5	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
8	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
14	M	KCNH2	N588K	IKr	Syncope	Ventricular fibrillation
19	M	KCNH2	E50D	IKr	Syncope	None

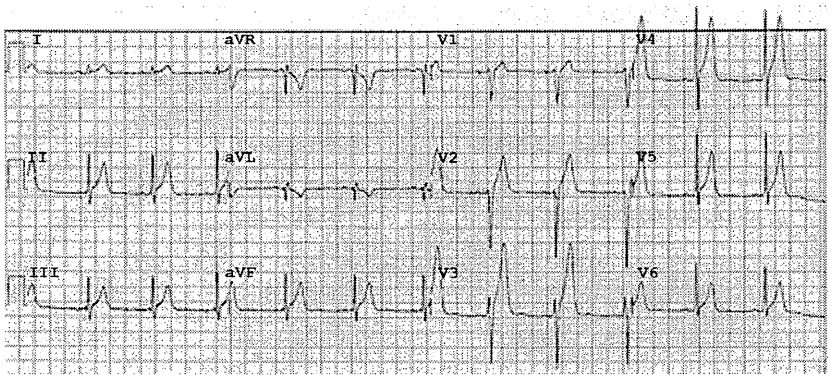

Figure 1 **Representative 12-Lead Electrocardiogram of the Short QT Syndrome**

Resting electrocardiogram (ECG) of a 15-year-old young male with aborted sudden cardiac death and a short QT interval (QT interval: 280 ms, QT interval corrected for heart rate [QTc]: 325 ms). There are peaked T waves in most of the precordial leads. The J point-to-T peak interval is 140 ms. There is early repolarization with upsloping ST segment in II, III aVF, and V_2 to V_6.

than those without aborted SCD (median: 7.3 years, IQR: 6.3 to 7.8 years vs. median: 5.3 years, IQR: 4.0 to 6.9 years, $p = 0.045$). A short J point-to-T peak (<120 ms) was more prevalent among the aborted SCD group (67% vs. 16%, $p = 0.032$) (Table 5). Five of these 6 patients had implantation of an ICD. In one instance, the parents declined an ICD for a 6-month-old young male (at the time of clinical presentation) with an ultra-short QT interval of 160 ms (QTc interval: 241 ms) who, at 80 months of follow-up, had no recurrent symptoms (Fig. 2). A positive family history of SQTS or SCD did not discriminate between aborted SCD and nonaborted SCD patients because of the high prevalence among the entire cohort. Early repolarization with upsloping ST segment in the anteroinferolateral leads was present in only 1 of the 6 patients with aborted SCD.

Therapy. ICD. Implantation of a cardioverter-defibrillator (ICD) was performed in 11 (44%) of 25 patients, in 6 as primary prevention (unexplained syncope in 2). Indications for ICD in the other 5 patients were aborted SCD or VF. Two (18%) patients had appropriate shocks: a 14-year-old young male (QT interval: 300 ms, QTc interval: 286 ms) with a history of aborted SCD while receiving quinidine at 9 mg/kg daily and a 14-year-old young male (QT interval: 248 ms; QTc interval: 252 ms) with a history of syncope and VF. The latter had no recurrent ICD appropriate shocks while taking quinidine. Two other patients had no shock and 7 (64%) had 1 or more inappropriate shocks. The underlying cause of inappropriate shocks was atrial fibrillation with rapid ventricular conduction (n = 1), sinus tachycardia (n = 3), SVT (n = 1), and ventricular lead fracture (n = 3), including 1 Sprint Fidelis lead (Medtronic, Minneapolis, Minnesota). There was an additional patient with a ventricular lead fracture 6 years after implantation that did not cause an inappropriate ICD shock. Of patients who received an ICD as primary prevention, 4 had inappropriate shocks.

MEDICAL THERAPY. Medical therapy was initiated in 10 (40%) of 25 patients, 4 of whom received multiple agents. Of the 4 patients with paroxysmal atrial fibrillation, 3 received quinidine therapy that proved unsuccessful in preventing recurrences of the arrhythmia. These patients were quite young, including an infant who also had recurrences while receiving propafenone and sotalol, a 5-year-old in whom flecainide also failed, and an 8-year-old. The remaining patient with atrial fibrillation was a 17-year-old young male (QT interval: 320 ms, QTc interval: 355 ms) (Fig. 3A) who was cardioverted at the time of ICD implantation, but continued to experience recurrences despite therapy with digoxin and propafenone. On treatment with digoxin and dofetilide, there was prolongation of the QT interval and return to sinus rhythm without symptomatic recurrences through follow-up (Fig. 3B). However, ICD interrogation identified asymptomatic, short episodes of atrial fibrillation. Two patients with a history of appropriate ICD shocks also received quinidine therapy. The first patient, a 14-year-old young male with aborted SCD, had a therapeutic shock while receiving quinidine 9 mg/kg daily. We were unable to confirm whether lack of compliance was the issue. The J point-to-T peak interval in this patient was 118 ms. He had a Gollob score of 8 with a QT interval of 300 ms (QTc interval: 286 ms). Genetic testing did not identify any known mutation. The second patient had no recurrent shocks while receiving quinidine therapy.

ARRHYTHMIAS ENCOUNTERED DURING FOLLOW-UP. Of the asymptomatic patients, only a 21-year-old man with an ICD as primary prevention had SVT resulting in inappropriate shocks and requiring ICD reprogramming. He had a modified Gollob score of 4. The other 10 asymptomatic cases with Gollob scores of 3 to 5 remained asymptomatic and arrhythmia-free during follow-up. In the group that was symptomatic at presentation, a 19-year-old man receiving no

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Table 5 Comparison of Patients With Versus Without Aborted Sudden Cardiac Death

Variable	Aborted SCD (n = 6)	No Aborted SCD (n = 19)	p Value
Patient age at presentation (yrs)	14 (14–15)	17 (8–18)	0.632
Age <12 yrs	1 (16.7%)	8 (42.1%)	0.364
Male	6 (100%)	15 (79%)	0.540
Follow-up duration (yrs)	7.3 (6.3–7.8)	5.3 (4.0–6.9)	0.045
Genetic mutation (n = 21)			
KCNH2	1 (20%)	1 (6.3%)	
KCNJ2	0	2 (12.5%)	
KCNQ1	0	1 (6.3%)	
Negative	4 (80%)	12 (75%)	
Family history			
SCD and/or SQTS	5 (83.3%)	16 (84.2%)	0.999
ECG parameters			
QT interval (ms)	280 (248–300)	295 (280–320)	0.261
QTc interval (ms)	300 (252–325)	312 (291–335)	0.323
QTc interval < 330 ms	5 (83.3%)	11 (57.9%)	0.364
J point-to-T peak interval	109 (80–140)	140 (120–160)	0.130
J point-to-T peak interval <120 ms	4 (66.7%)	3 (15.8%)	0.032
Early repolarization	1/6 (17%)	11/18 (61%)	0.155
Medical therapy with quinidine	3 (50%)	6 (31.6%)	0.344
Documented arrhythmia on follow-up			
Ventricular fibrillation	1 (16.7%)	0	
Polymorphic VT	1 (16.7%)	0	
Atrial fibrillation	0	3 (15.8%)	
SVT	0	1 (5.3%)	
ICD	5 (83.3%)	6 (31.6%)	0.056
Appropriate shocks	2 (40%)	0	
Inappropriate shock	3 (60%)	4 (66.7%)	
Complications*	5 (100%)	4 (66.7%)	

Values are median (interquartile range) or n (%). *Including inappropriate shocks.
SVT = supraventricular tachycardia; other abbreviations as in Tables 1 and 3.

medical therapy and with a history of aborted SCD experienced 2 episodes of nonsustained polymorphic ventricular tachycardia that terminated spontaneously. All cases with atrial fibrillation required ongoing therapy with cardioversion, medical treatment with different antiarrhythmic agents, or both. A 3-month-old young female with an ultra-short QT of 200 ms (QTc interval: 275 ms) had a history of marked sinus bradycardia since birth and atrioventricular node dysfunction with a Wenckebach cycle length of 500 ms. The patient demonstrated atrial fibrillation at 4 days of age, requiring cardioversion. A ventricular pacemaker was implanted at 6 days of age. Despite antiarrhythmic therapy, it eventually progressed into permanent atrial fibrillation. A 5-year-old young female with an ultra-short QT of 172 ms (QTc interval: 194 ms) had mechanically induced atrial and VF during insertion of a Swan Ganz catheter.

Discussion

To our knowledge, this is the longest follow-up cohort of patients with SQTS reported in the literature. It also represents the largest series of pediatric SQTS patients, because the average age in this cohort was 13 years.

Our cohort was predominantly male (84%), reflecting a sex-specific prevalence and possible greater vulnerability to SQTS in young males as compared with young females. Eighty-four percent of patients had a personal or familial history of cardiac arrest. More than half of our patients had symptoms, including aborted SCD (24%) and syncope (16%). The most common symptomatic presentation was cardiac arrest. An additional 11 cases (44% of cohort) were identified through cascade family screening. Twenty percent of cases were identified to have disease-causing mutations. Our cohort included a 6-year-old young male with aborted SCD and a QT interval of 160 ms, the shortest QT interval reported to date. In addition, we report 3 children younger than 8 years with recalcitrant atrial fibrillation and ultra-short QT intervals ranging from 172 to 200 ms and 1 patient, an infant with a QT of 200 ms (QTc interval: 275 ms), who had coexisting sinus and atrioventricular node dysfunction. This patient had sinus bradycardia at birth and demonstrated slow atrial fibrillation at 4 days of age. To our knowledge, the latter clinical scenario associated with a V141M mutation in the KCNQ1 gene has not been reported with SQTS. Another unique finding in this young population has been the high incidence of inappropriate shocks, affecting 64% of ICD recipients, which far exceeded appropriate shocks.

A previously reported study presented the clinical characteristics and outcomes in an adult population of SQTS patients (median age: 26 years) (19). Similar to the observations of our pediatric cohort, most clinically affected adults were men (75%), cardiac arrest as a first presentation was relatively common (32%), a family history of SQTS was present in 50% of patients, and disease-causing mutations were found in 23% of probands. In contrast, our pediatric cohort tended to have a shorter QTc interval (average: 304 ms vs. 314 ms), and although adult and pediatric ICD recipients both received a high inappropriate shock rate, this was more common in pediatric patients (64% vs. 33%).

Gollob et al. (16) proposed diagnostic criteria for SQTS. We found that a modified Gollob score, which excluded points for clinical events, may be useful in identifying patients at a higher risk for unexplained syncope, atrial fibrillation, or aborted SCD. Our patients with a history of these clinical events had a median modified score of 5 (range: 4 to 6) as compared with a median of 4 (range: 4 to 5) in patients who remained asymptomatic (except 1 case of SVT). Patients with a modified Gollob score of 3 (or Gollob score of <5) had a good prognosis during follow-up in this study. Only 1 (7%) of 14 symptomatic patients had a low modified Gollob score of 3.

SQTS is considered a rare electrical abnormality, and recognition of this condition as a cause of unexplained SCD in young children is uncommon, although perhaps underrecognized. A reported series of adult patients with idiopathic VF were noted to have a mean QTc value of 371 ms, significantly less than the QTc value of healthy sex- and age-matched controls (20). These observations suggest that

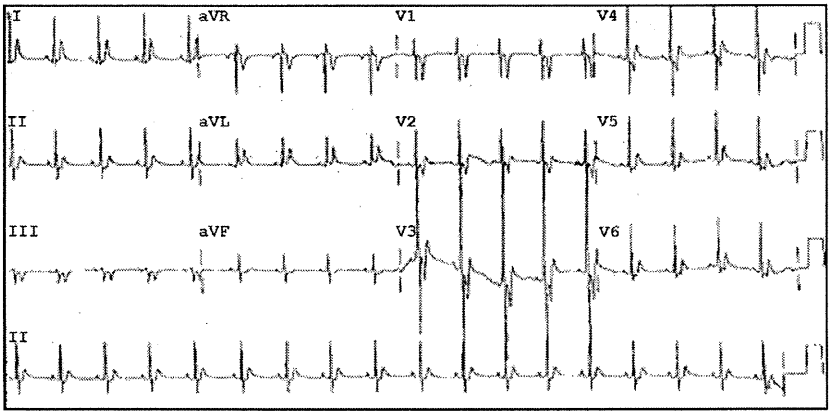

Figure 2 **Extreme Abbreviation of QT Interval in a Young, Symptomatic Child**

An ultra-short QT interval of 160 ms (QTc interval: 241 ms) in a 6-month-old young male at the time of clinical evaluation after cardiac arrest.

less extreme values of short QTc interval may be part of the SQTS disease spectrum.

Aborted SCD affected 6 of our patients (24%), 5 of them at 15 years of age or younger. One of the current therapeutic options for patients with SQTS includes implantation of an ICD (21–23). Six of our patients received an ICD for primary prevention; however, 4 experienced 1 or more inappropriate ICD shocks. Previous studies have reported an increased risk for inappropriate ICD therapy because of oversensing of short-coupled and prominent T waves resulting in T-wave oversensing (24). In our young cohort with SQTS, inappropriate shocks far exceeded appropriate shocks. Most of our patients had inappropriate shocks secondary to atrial tachycardias, including sinus tachycardia (n = 3), SVT (n = 1), and atrial fibrillation (n = 1). Inappropriate therapies resulting from rapid atrial arrhythmias may be prevented by programming device therapies for heart rates exceeding 210 beats/min, although a formative assessment is needed to evaluate the efficacy of such an approach. In addition, we observed a high prevalence of ventricular lead fracture of 36% (4 of 11 cases) with most (3 of 4) resulting in inappropriate ICD shocks. The high prevalence of ventricular lead fracture in part may be the result of the patients' young ages at implantation. These points together highlight our concerns regarding the use of ICD therapy in asymptomatic young patients.

We identified a higher prevalence of short J point-to-T peak interval (<120 ms) in symptomatic (42.9%) versus asymptomatic patients (9.1%). However, because of the small number of cases, the difference did not reach statistical significance. Watanabe et al. (25) reported a high prevalence (65%) of early repolarization in patients with SQTS that was associated with arrhythmic events. In their cohort, early repolarization was localized in either inferior leads, lateral leads, or both, but the ST segment contour was not described in their paper. Early repolarization with upsloping morphological features can be a benign ECG finding (26), whereas a horizontal or downsloping ST segment may be associated with VF (27). Early repolarization also was observed in a high percentage of our cohort (50%), and it was localized in anterior, inferior, and lateral leads, or in a combination thereof. This ECG feature was not significantly different between our symptomatic (43%) and asymptomatic (60%) patients. None of our patients with early repolarization had a horizontal or downsloping pattern. Only 1 of our 6 cases of aborted SCD showed early repolarization.

Five of our patients, all symptomatic, had genetic mutations associated with SQTS. The yield of genetic mutation detection was 24% for index patients who underwent genetic testing. This compares with the 23% incidence reported in the literature (16).

Quinidine has been suggested as one of the mainstay therapies for SQTS because of its ability to offset the extreme shortening of repolarization that occurs in SQTS (28). In this cohort, quinidine proved ineffective in managing atrial fibrillation in those patients with frequent recurrences. In addition, while receiving a low dose of quinidine, one patient experienced a therapeutic ICD shock. Therefore, the effectiveness of this antiarrhythmic agent in young SQTS patients awaits further investigation.

Study limitations. Although we describe the largest population of pediatric patients with SQTS with the longest reported clinical follow-up, event rates and risks in later decades of life remain unknown. As a relatively rare or perhaps under-recognized disease, our cohort included only 25 patients. Thus, we must be cautious in reaching conclusions based on such a small group.

Conclusions

SQTS in the pediatric population is associated with a high risk of aborted SCD. The diagnosis seems more common in young males similar to observations in adult SQTS patients. This may reflect protection from ultra-short QT intervals in

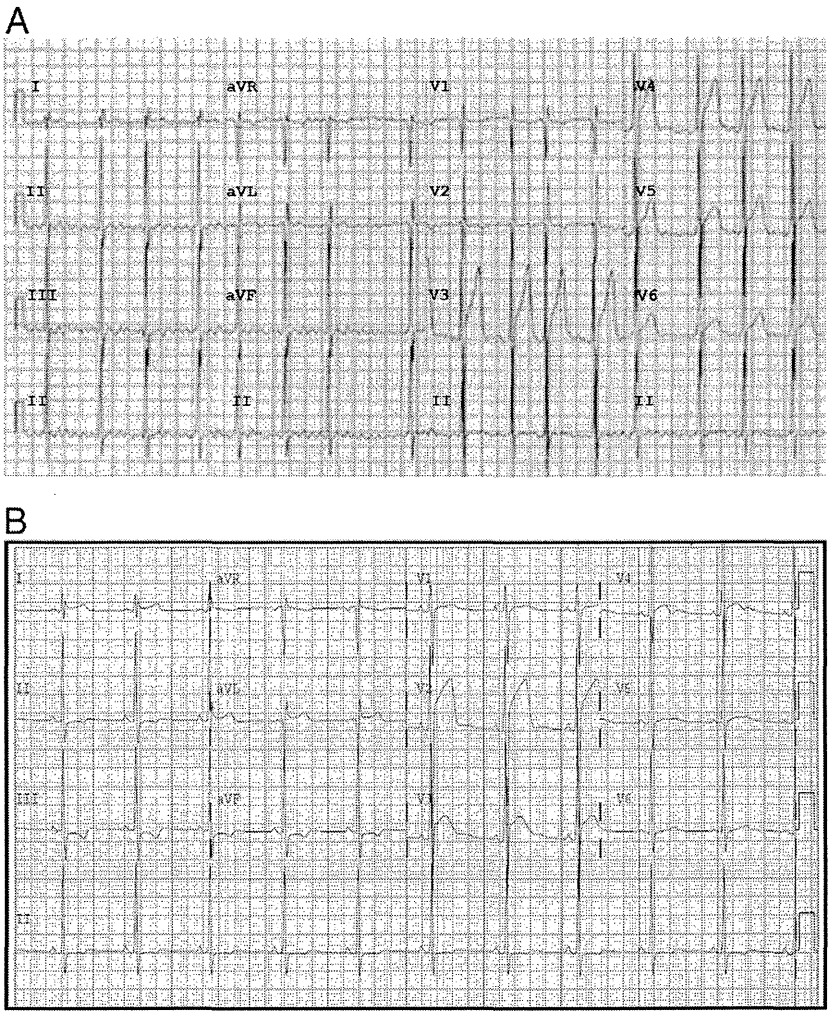

Figure 3 **Atrial Fibrillation and the Short QT Syndrome in a 17-Year-Old Young Male Resulting in Conversion to Sinus Rhythm and Prolongation of the QT Interval With Antiarrhythmic Therapy**

(A) 12-lead ECG of a symptomatic 17-year-old young male with atrial fibrillation. There is a short QT interval (QT interval: 320 ms, QTc interval: 355 ms), peaked T waves, and early repolarization. **(B)** After treatment with dofetilide and digoxin, there was prolongation of the QT interval (QT interval: 380 ms, QTc interval: 380 ms). The patient remained asymptomatic and on sinus rhythm except for short bouts of atrial fibrillation.

women because of the QT prolonging effects of estrogen (29). A modified Gollob score may be useful in identifying patients at a higher risk of clinical events and may prove useful for risk stratification, although larger cohort studies are necessary. Although ICD therapy proved useful in some patients, it was fraught with inappropriate shocks. One of 2 appropriate ICD shocks occurred despite a low dose of quinidine. Quinidine monotherapy did not prove to be effective in treating atrial fibrillation.

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Key Words: arrhythmias ▪ atrial fibrillation ▪ short QT syndrome ▪ sudden cardiac death.

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ORIGINAL ARTICLE

Usefulness of scintigraphy to predict electrical storms in severe idiopathic dilated cardiomyopathy

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Abstract
Background Although several predictors of an electrical storm (ES) are indicated in patients with idiopathic dilated cardiomyopathy (IDCM), whether the severity of the myocardial tissue damage (SMTD) evaluated by myocardial perfusion SPECT (MPS) has an association with an ES remains unclear. The purpose of this study was to elucidate the clinical significance of SMTD for the prediction of ES in IDCM patients with an ICD.
Methods Thirty-seven (27 men, mean age 58 ± 15 years) IDCM patients receiving ICD implantations for secondary prevention with preoperative MPS were enrolled in this study. The medical history, physical and laboratory findings, electrocardiograms, echocardiograms and MPS findings were evaluated. The SMTD was assessed by the summed scores of 17 segments using a 4-point system (0, normal ~3, severe defect).
Results During a mean follow-up of 43.9 ± 30.7 months, an ES developed in 12/37 (32.4 %) patients. The SMTD score predicted an ES with a 92 % sensitivity and 56 % specificity, at a cut-off score of 10. In addition, a multivariate analysis showed that the SMTD score remained an independent predictor of an ES (HR 1.09/score 1 increase, 95 % CI 1.01–1.19, $p = 0.02$). The SMTD score was significantly associated with three indices of late potentials on the signal-averaged electrocardiograms, and was significantly higher in patients with positive late potentials ($p = 0.0006$).
Conclusion SMTD score assessed by MPS has a strong correlation to the late potentials and higher SMTD score may increase the risk of ES among patients with IDCM and an ICD.

Keywords Idiopathic dilated cardiomyopathy · Implantable cardioverter defibrillator · Electrical storm · SPECT · Myocardial tissue damage

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Introduction

Implantable cardioverter defibrillators (ICDs) provide an established therapeutic option for reducing the risk of sudden cardiac death, and have a high success rate in terminating life-threatening ventricular arrhythmias including ventricular tachycardia (VT) or ventricular fibrillation (VF) [1, 2]. About 40–60 % of patients with an ICD will receive an appropriate ICD therapy for VT/VF within 3 years of the implantation [3–5]. Such therapy is usually limited to antitachycardia pacing or a small amount of shocks for targeted ventricular tachyarrhythmias. However, some

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patients experience multiple shock therapies, which significantly compromise the quality of life of ICD recipients and increase the risk of subsequent death [6].

Due to the increase in the number of patients with ICD indications, electrical storm (ES), which is defined as 3 or more separate episodes of ventricular tachycardia (VT) and/or ventricular fibrillation (VF) terminated by ICD therapies within 24 h, have become an important issue because of the clinical, psychological and economical consequences involved. Although we and several investigators have reported the incidence, predictive factors and clinical prognosis of an ES in patients with idiopathic dilated cardiomyopathy (IDCM) [1, 3–5, 7–9], the significance of the severity of the myocardial tissue damage (SMTD) as a predictor of an ES remains unclear. We attempted to elucidate the clinical value of SMTD in predicting an ES in patients with IDCM and an ICD.

Methods

Study population

Forty-eight consecutive IDCM patients received an ICD for secondary prevention between 1998 and 2004 at the National Cerebral and Cardiovascular Center. In addition to the examinations necessary for the precise diagnosis, MPS prior to the ICD implantation was routinely performed in IDCM patients during this period unless it was rejected by the patient. The medical records including the clinical characteristics, medications, and electrocardiographic, echocardiographic and MPS findings were analyzed.

Patients with a history of hypertension were excluded from this study to carefully rule out hypertensive heart disease. Coronary angiography and echocardiography were performed in all patients to rule out ischemic cardiomyopathy and valvular heart disease. Other modalities including specific biochemical tests, magnetic resonance imaging, nuclear imaging, cardiac biopsy, and genetic testing were added if required according to the patient's history, to exclude other secondary cardiomyopathies including infectious cardiomyopathy, toxic cardiomyopathy, peripartum cardiomyopathy, tachycardia-mediated cardiomyopathy, autoimmune cardiomyopathy, infiltrative cardiomyopathy, and hereditary cardiomyopathy. Finally, patients with diffuse left ventricular dysfunction and enlargement of the left ventricle with an unknown etiology were defined as having IDCM.

In these patients, an ICD was implanted for secondary prevention of sudden cardiac death after one or more episodes of confirmed sustained ventricular tachyarrhythmias or under the context of any presumed tachyarrhythmic syncopal attacks. The implanted devices included Medtronic 7221CX, 7223CX, 7227CX, 7229CX, 7271, 7273, and 7278, and CPI/Guidant 1790 and 1861 devices. The ICD was programmed according to the documented or induced arrhythmia with at least two detection zones. Antitachycardia pacing including more than one burst pacing and one ramp pacing therapy followed by cardioversion were programmed in the VT-zone, whereas the maximum shocks were programmed in the VF-zone. Written informed consent was given before the ICD implantation.

The study protocol according to the ethical guidelines of the 1975 Declaration of Helsinki was approved by the Institutional Review Board at National Cerebral and Cardiovascular Center, and were announced to the patients. The patient privacy was completely protected by anonymization of the entire data.

Definition of ES

Three expert electrophysiologists randomly reviewed the intracardiac electrograms to avoid delivering inappropriate therapies. The occurrence of 3 or more separate episodes of VT/VF terminated by an appropriate ICD therapy within a 24-h period was defined as an ES [8]. The appropriate ICD therapy consisted of antitachycardia pacing as well as low- and high-energy shocks for the targeted ventricular tachyarrhythmias. Repetitive ineffective shocks were not categorized as an ES.

Follow up

The patient follow-up started after the implantation. The patients visited the outpatient clinic every 1–2 months as a follow-up with a routine blood test and electrocardiogram. Furthermore, the ICD was checked every 3–6 months. They were also encouraged to visit whenever palpitations, pre-syncope or shocks occurred. The interrogation part of the device follow-up was performed to evaluate the number and type of episodes from the stored intracardiac-electrograms during each check. Patients encountering an ES were admitted to the hospital for a detailed investigation of the cause including a blood analysis (electrolytes, blood cell count, and the thyroid, creatinine, C-reactive protein, creatinine kinase, and troponin levels), echocardiography and coronary angiography if necessary.

SMTD scores using myocardial perfusion SPECT

Rest MPS was performed at least 1–3 months before the ICD implantation with a stable condition of chronic heart failure (CHF). One hour after the intravenous injection of 600 MBq of technetium-99m (^{99m}Tc) sestamibi, the patients consumed a light meal or milk before image acquisition to remove the tracer retention in the liver and

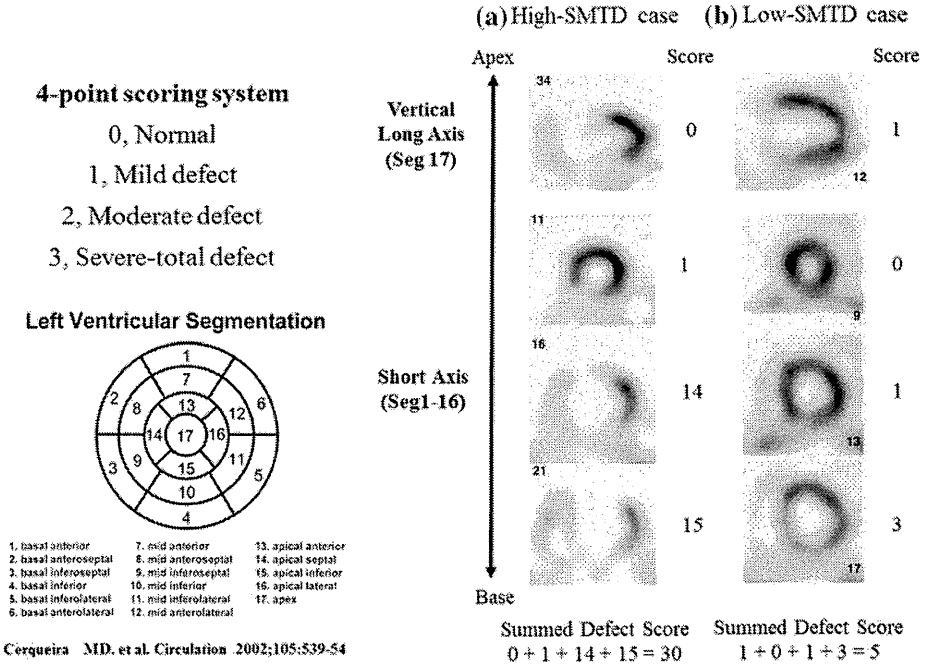

Fig. 1 Semiquantitative visual analysis using a myocardial 17-segment model. Tracer uptake in each segment was evaluated using a 4-point scoring system (0, normal; 1, mild; 2, moderate; 3, severe reduction or absence of radioisotope uptake). The short-axis view was used for assessing segments *1–16*, and the vertical long-axis view was used for assessing segment *17*. **a** Typical case with high-SMTD scores (summed defect score = 30). Severe-total defects were identified through the basal to mid-ventricular levels, especially in anterior, inferior, and septal walls. This patient experienced an electrical storm. **b** Typical case with low-SMTD scores (summed defect score = 5). Only mild defects were seen in basal level and apex. This patient did not experienced an electrical storm

gallbladder. Thirty projection images were obtained over 180° in 6° increments with 50 beats per view, using a dual-headed SPECT system (VERTEX; ADAC Laboratories, Milpitas, CA, USA) equipped with a low-energy general-purpose collimator. The image resolution in the transaxial plane was 16 mm full-width at half-maximum and data were stored in a 64 × 64 matrix. Energy discrimination was centered on 141 keV with a 20 % window. Transaxial tomograms were generated from the projection data and oblique angle tomograms were reconstructed using a ramp filter and a Butterworth filter (order 8, cut-off 0.27 cycle/pixel).

SPECT images were semiquantified using a myocardial 17-segment model. Segments 1–16 were assigned to four evenly spaced regions of apical slices, with six each of mid-ventricular and basal slices in the short-axis views. Segment 17 was assigned to the extreme tip of the ventricle where there is no longer cavity present assessed by vertical long-axis view (Fig. 1) [10]. The tracer uptake in each segment was scored using a 4-point system (0, normal; 1, mild; 2, moderate; 3, severe reduction or absence of radioisotope uptake). A summed defect score was obtained by adding each score of the 17 segments, and served as an index of the severity of the myocardial tissue damage. Three experienced observers, who were blinded to the clinical findings, determined the summed defect scores of each segment. The averaged score was adopted for analysis as a SMTD score. Examples of patients with typical high- and low-SMTD scores assessed by one observer were represented in Fig. 1.

Signal-averaged ECG

Ventricular late potentials (LPs) were analyzed using a signal-averaged ECG system (Arrhythmia Research Technology model 1200 EPX, Austin, TX, USA). The analysis was based on quantitative time-domain measurements of the filtered vector magnitude of orthogonal Frank X, Y, and Z leads. This system consisted of a vector magnitude with a bidirectional bandpass filter set between 40 and 250 Hz combined with the standard bipolar orthogonal (X, Y, Z) leads. Signals from 200 to 300 beats were averaged to obtain a diastolic noise level of <0.5 μV. The following parameters were assessed using a computer algorithm: (1) total filtered QRS (TFQRS) duration, (2) root-mean-square voltage of the terminal 40 ms of the filtered QRS complex (RMS40), and (3) duration of the terminal low amplitude signals of <40 μV in the terminal-filtered QRS complex (LAS40). An LP was considered to be positive when at least two of the following criteria were met: (1) TFQRS

>120 ms, (2) RMS40 <20, and (3) LAS40 >38 ms [11] in patients with a normal QRS duration, and (1) TFQRS >170 ms, (2) RMS40 <20, and (3) LAS40 >45 ms [12] in patients with bundle blanch block.

Statistics

All data were statistically analyzed using JMP 7.0.1 software. Data are expressed as the mean ± standard deviation (SD) for continuous variables, and as frequencies and ratios (%) for categorical variables. The significance of the baseline variables with respect to the outcome was assessed using univariate Cox proportional hazards models. A multivariate analysis was performed with an adjustment for the age, sex, BMI, NYHA functional class, and LVEF. Observations were censored at the time of the last known follow-up when an ES did not occur or at the time of death. A receiver operating characteristic (ROC) curve analysis was used to determine the appropriate cut-off value of the SMTD score. Event-free survival curves were calculated according to the Kaplan–Meier method. The significance of differences between curves was determined using a log rank test. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Finally, 37 (27 men and 10 women) patients who agreed to undergo MPS were enrolled in this study. Table 1 shows the baseline characteristics of the study patients. The mean age at the time of the ICD implantation was 58 ± 15 years and the mean NYHA functional class was 2.7 ± 1.1. Over 80 % of the patients were prescribed with beta-blockers, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs). Class III antiarrhythmics were prescribed to 23 (59.5 %) patients. When class III antiarrhythmics were used, amiodarone was selected first, and changed to sotalol in case of amiodarone intolerance. Single- and dual-chamber devices were implanted in 14 (37.8 %) and 23 (62.1 %) patients, respectively.

Electrical storm

During a mean follow-up of 43.9 ± 30.7 months (median of 42.0 months, ranging from 1 to 118 months), 12 (32.4 %) patients experienced at least one ES episode (mean 5 ± 5.1 episodes; median of 3.5 episodes per patient) and 7 (58.3 %) of those 12 experienced two or more. The mean duration between the first ES occurrence and the ICD implantation was 30.8 ± 33.6 months (median 17.0 months, ranging from 1 to 84 months). The ES was apparently generated by exacerbated heart failure in 3 (25.0 %) patients, low potassium levels in 2 (16.7 %), infection in 1 (8.4 %), and non-specific causes in the remaining 6 (50 %).

Risk factors for an ES

Tables 2 and 3 show the results of the univariate and multivariate analyses regarding the occurrence of an ES. An univariate Cox proportional regression analysis indicated that the NYHA functional class ($p = 0.04$), monomorphic VT as an index arrhythmia ($p = 0.03$), QRS duration ($p = 0.04$) and QTc interval ($p = 0.02$) on the electrocardiogram, LVDd ($p = 0.03$) and posterior wall thickness ($p = 0.04$) on the echocardiogram, and the SMTD on the MPS ($p = 0.01$) were significant predictors of an ES occurrence. However, when these parameters were adjusted for the age, sex, BMI, NYHA functional class, and LVEF, only the SMTD on the MPS remained as a significant predictor of an ES occurrence ($p = 0.02$, HR 1.09/score 1 increase, CI 1.01–1.19).

Significance of the SMTD score as a predictor of an ES

The sensitivity–specificity analysis used receiver operating characteristics (ROC) curves, with a cut-off value of the SMTD score being set at 10 to optimize the capability of predicting an ES (Fig. 2). At a cut-off score of 10, the area under the curve was 0.802, and the SMTD score predicted an ES with 92 % sensitivity, 56 % specificity, and positive and negative predictive values of 52 % and 94 %. Figure 3 shows the Kaplan–Meier curves for the freedom from ES events between the groups with SMTD scores of ≥10 and <10. The ES event-free rate at 1, 3, and 5 years was 76.4, 66.2, and 57.9 % in the group with an SMTD score of ≥10, and was stable at 93.3 % in those with an SMTD score of <10. The patients with IDCM had a significantly higher risk of an ES occurrence when the SMTD score was ≥10.

Relationship between the SMTD score and LPs

Thirty-six (97.3 %) patients received a signal-averaged ECG to assess late potentials. Figure 4 shows the relationship between the SMTD score and LPs. Among 36 patients, positive LPs were observed in 22 (61.1 %), and the SMTD score was significantly larger in the patients with LPs than in those without (16.1 ± 9.4 and 6.1 ± 4.7, respectively; $p = 0.0006$). In addition, the SMTD score was significantly correlated with each index of the SAECG such as the TFQRS ($r^2 = 0.27$, $p = 0.0013$), LAS40

Table 1 Patient characteristics

Age (years)	58 ± 15
Sex, male	27/37 (73.0 %)
BMI	21.7 ± 2.9
NYHA class I	2.7 ± 1.1
I, II, III, IV	6 (16.2 %), 9 (24.3 %), 12 (32.5 %), 10 (27.0 %)
History of heart failure	21/37 (56.8 %)
SMTD score	12.4 ± 9.5
Monomorphic VT as the index arrhythmia	23/37 (62.2 %)
Electrocardiography	
QRS duration (ms)	129 ± 39
QTc interval (ms)	493 ± 53
Echocardiography	
LVDd (mm)	67.1 ± 10.1
LVDs (mm)	56.4 ± 12.4
IVST (mm)	7.0 ± 1.1
PWT (mm)	6.9 ± 1.0
LVEF (%)	25.2 ± 8.9
Medications	
β-blockers	30/37 (81.1 %)
Class III antiarrhythmics	23/37 (59.5 %)
Spironolactone	18/37 (48.6 %)
Digitalis	19/37 (51.4 %)
Diuretics	28/37 (75.7 %)
ACEIs/ARBs	30/37 (81.1 %)

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor antagonists, *BMI* body mass index, *IVST* interventricular septum thickness, *LVDd* left ventricular diameter of end-diastole, *LVDs* left ventricular diameter of end-systole, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PWT* posterior wall thickness, *SMTD* severity of the myocardial tissue damage, *VT* ventricular tachycardia

Table 2 Univariate analysis to predict ES

	Univariate *p* value	HR	95 % CI
Age	0.08	1.04	1.00–1.10
Sex, female	0.48	1.56	0.42–4.98
BMI	0.47	0.93	0.74–1.13
NYHA class	0.04	1.92	1.02–4.09
History of heart failure	0.26	1.96	0.61–7.40
SMTD score	0.01	1.09	1.01–1.19
Monomorphic VT as an index arrhythmia	0.03	4.61	1.17–30.73
Electrocardiography			
QRS duration (ms)	0.04	1.02	1.00–1.03
QTc intervals (ms)	0.02	1.01	1.00–1.02
Echocardiography			
LVDd (mm)	0.03	1.07	1.01–1.14
LVDs (mm)	0.05	1.05	1.00–1.10
IVST (mm)	0.46	0.81	0.46–1.39
PWT (mm)	0.04	0.53	0.27–0.98
LV EF (%)	0.21	0.96	0.89–1.02
Medication			
β-blockers	0.39	0.54	0.16–2.47
Class III antiarrhythmics	0.98	0.99	0.31–3.35
Spironolactone	0.24	2.00	0.62–6.93
Digitalis	0.48	1.51	0.48–5.11
Diuretics	0.25	2.30	0.60–15.13
ACEIs/ARBs	0.82	1.18	0.31–7.71

ACEIs angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor antagonist, *BMI* body mass index, *CI* confidential interval, *IVST* interventricular septum thickness, *HR* hazard ratio, *LVDd* left ventricular diameter of end-diastole, *LVDs* left ventricular diameter of end-systole, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PWT* posterior wall thickness, *SMTD* severity of myocardial tissue damage, *VT* ventricular tachycardia

($r^2 = 0.39$, $p < 0.0001$), and log RMS40 ($r^2 = 0.32$, $p = 0.0004$).

Discussion

The main finding of the present study was that one-third of patients with IDCM and an ICD experienced an ES during the follow-up and a SMTD score was significantly associated with the occurrence of an ES in these patients.

Incidence of ES

Twelve (32.4 %) patients experienced at least one ES episode during a mean follow-up of 43.9 ± 30.7 months (median 42.0 months, ranging from 1 to 118 months). In general, an ES occurs in 4–28 % [1, 3, 7, 8] of ICD recipients. The incidence of an ES is lower when ICDs are placed for primary prevention compared to secondary prevention. In a MADIT-II sub-study of 719 patients receiving ICDs for primary prevention, 4 % developed ESs over an average of 20.6-month period [8]. In another trial, 20 % of the patients who received ICDs for secondary prevention experienced an ES during a 31-month period [13]. Especially when focusing on IDCM patients with ICDs for secondary prevention, 28 % of the patients experienced an ES during a 32.5-month period [1]. Although the incidence seemed to be relatively higher in the present study compared to several past literatures, this discrepancy could be explained by the fact that the patients in this study were only IDCM patients with a low EF referred to our institution for the treatment of advanced CHF, and, in addition, they were followed up longer.

Table 3 Multivariate analyses adjusting for the age, sex, BMI, NYHA functional class, and LVEF

	Adjusted *p* value	HR	95 % CI
History of heart failure	0.17	0.18	0.01–2.05
SMTD score	0.02	1.09	1.01–1.19
Monomorphic VT as the index arrhythmia	0.17	3.10	0.65–24.65
Electrocardiography			
QRS duration (ms)	0.09	1.01	0.99–1.03
QTc intervals (ms)	0.07	1.01	1.00–1.02
Echocardiography			
LVDd (mm)	0.13	1.08	0.99–1.21
LVDs (mm)	0.16	1.08	0.97–1.23
IVST (mm)	0.69	1.17	0.53–2.57
PWT (mm)	0.10	0.52	0.21–1.14
Medication			
β-blockers	0.46	0.56	0.13–2.91
Class III antiarrhythmics	0.69	0.78	0.23–2.86
Spironolactone	0.49	1.52	0.46–5.51
Digitalis	0.59	1.42	0.40–5.31
Diuretics	0.17	3.05	0.66–24.20
ACEIs/ARBs	0.85	0.85	0.20–5.86

ACEIs angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor antagonist, *BMI* body mass index, *CI* confidential interval, *IVST* interventricular septum thickness, *HR* hazard ratio, *LVDd* left ventricular diameter of end-diastole, *LVDs* left ventricular diameter of end-systole, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PWT* posterior wall thickness, *SMTD* severity of myocardial tissue damage, *VT* ventricular tachycardia

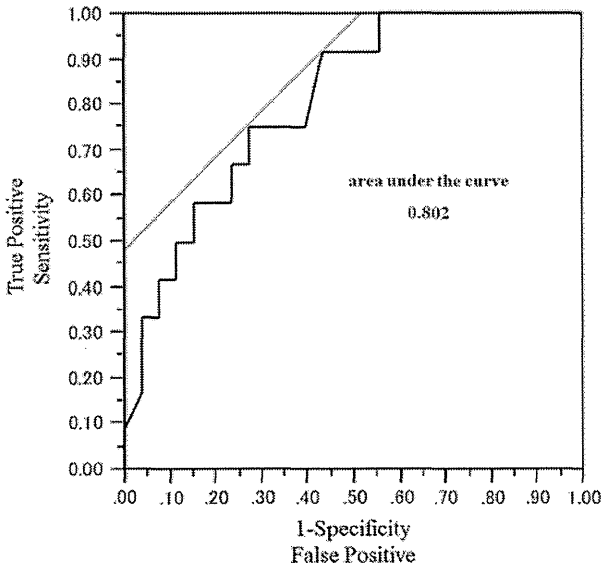

Fig. 2 A sensitivity–specificity analysis using receiver operating characteristics (ROC) curves. A cut-off value of the SMTD score set at 10 optimized the capability of predicting an ES

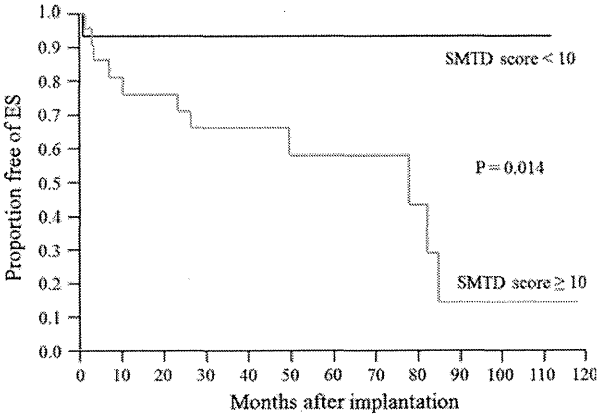

Fig. 3 Kaplan–Meier curves of the freedom from ES events between the groups with SMTD scores of ≥10 and <10 ms. The risk of an ES occurrence was significantly higher among the IDCM patients with SMTD scores of ≥10 than in those with scores of <10 ($p = 0.014$). *SMTD* severity of the myocardial tissue damage

SMTD score as a predictor of an ES

A higher SMTD score remained as a significant predictor of an ES in the multivariate analysis. The risk of an ES increased by 9 % for each additional 1-point increase in the SMTD score ($p = 0.02$, HR 1.09/1 increase in the score, CI 1.01–1.19). The optimized cut-off SMTD score determined from the ROC curves for differentiating patients with and without an ES was 10 in this study. At this cut-off score, the SMTD predicted an ES with 92 % sensitivity, 56 % specificity, and positive and negative predictive values of 52 % and 94 %.

As far as we know, this is the first report to describe an association between the SMTD and ES occurrence in IDCM patients with an ICD. However, several reports have indicated the significance of the SMTD as a predictor of ventricular tachyarrhythmias or the prognosis in patients with an old myocardial infarction (OMI). De Sutter et al. [14] reported that the extent of scarring determined by myocardial perfusion imaging can separate patients with coronary artery disease into high- and low-risk groups in terms of recurrent ventricular arrhythmias and cardiac hospitalization after the ICD implantation. Nishisato et al. [15] demonstrated that impairment of cardiac sympathetic innervation and myocardial perfusion is related to lethal arrhythmic events leading to sudden death, and the combined assessment of these might be useful for identifying patients who need a prophylactic ICD. Morishima et al. [16] showed that perfusion volume defects determined by Tc-99m tetrofosmin scintigraphy in patients with an OMI is a pivotal predictor of future lethal arrhythmic events and sudden cardiac death. They also suggest the mechanism of arrhythmogenicity using signal-averaged ECGs. A larger

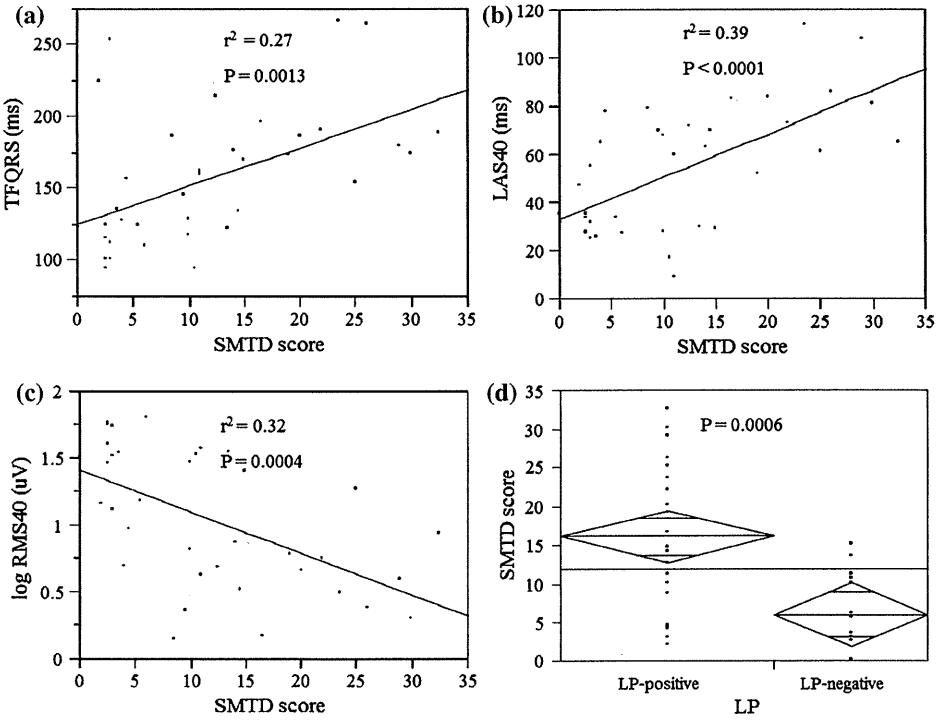

Fig. 4 Relationship between the SMTD score and late potentials. The SMTD score was significantly correlated with the **a** TFQRS ($r^2 = 0.27$; $p = 0.0013$), **b** LAS40 ($r^2 = 0.39$; $p < 0.0001$), and **c** logRMS40 ($r^2 = 0.32$; $p = 0.0004$). **d** Moreover, the SMTD score was significantly larger in the patients with than in those without late potentials (16.1 ± 9.4 and 6.1 ± 4.7, respectively; $p = 0.0006$). *LAS40* duration of the terminal low amplitude signals of <40 μV in the terminal-filtered QRS complex, *LP* late potentials, *SMTD* severity of the myocardial tissue damage, *TFQRS* total filtered QRS duration, *RMS40* root-mean-square voltage of the terminal 40 ms of the filtered QRS complex

area of the volume defect is highly correlated with an increasing prevalence of LPs, which suggests the existence of a greater arrhythmogenic substrate increasing the risk of ventricular arrhythmias. Our findings from the SAECG also suggested the association between the LPs and SMTD score (Fig. 4). All three indices of the LPs were significantly correlated with the SMTD score from the MPS ^{99m}Tc MIBI scintigraphy. Thus, lethal ventricular arrhythmias including VT and VF are considered to arise on the basis of an arrhythmogenic substrate comprised of necrotic, fibrotic or degenerative myocardial tissue. However, other modulating factors such as ischemia, drugs, heart electrolytes, autonomic nerve activity and stress, or triggers such as premature ventricular contractions might be also taken into consideration. An arrhythmogenic substrate can be visualized as a defect area on the MPS [17]. We previously reported the significance of the SAECG in predicting an ES [9]. However, the data of the SAECG were, unfortunately, not obtained in all patients, and the strong correlation of these SAECG parameters and the SMTD score made it impossible to reveal the independent significance of each other in the small study population.

Other predictors of an ES

Although the clinical value of LVEF in predicting an ES has not fully been elucidated, several reports have revealed the significant association between LVEF and an ES [1, 3, 4, 7, 18–21]. Bausch et al. [1] revealed that a low LVEF (<40 %) is one of the best predictors of an ES in patients with IDCM, and Lunati et al. [18] showed that an LVEF <25 % is significantly associated with VT/VF clusters in patients with a biventricular ICD. However, Narasimhan et al. [20] demonstrated that the role of the LVEF is not always a strong predictor and is limitedly useful in patients with coronary artery disease. In the present study, the LVEF was not significantly associated with the occurrence of an ES when analyzed with the SMTD by a multivariate analysis. The discrepancies between several studies and the present study regarding the LVEF might be explained by the difference in the population size, severity or type of underlying disease, type of device [ICD or cardiac resychronization therapy defibrillator (CRT-D)], or the definition of an ES [1, 3, 4, 7, 8, 18–21].

Monomorphic VT is still controversial as a predictor of an ES. However, several studies support its significance in nonischemic dilated cardiomyopathy [1, 18]. While the mechanism responsible for the clustering of tachycardia is uncertain, clustering may be facilitated by the presence of ventricular scar [22, 23], and this mechanism is theoretically acceptable. In the present study, monomorphic VT was one of the predictors of an ES in the univariate analysis, but it did not remain so in the multivariate analysis. The small population of our study design may affect the results in this point.

Clinical implications

Several investigators have examined the prognostic significance of VT/VF episodes, and most have found that the development of electrical clusters or storms identifies ICD recipients with a transiently higher risk of death [18]. Stratifying the risk of an ES with the SMTD score enables us to achieve the appropriate choice of medication and careful follow-up in specific patients. In addition, recent reports revealed the possibility of empirical ablation techniques for substrate modification to prevent or reduce VT/VF episodes [24, 25]. However, further work up should be required in this field.

Study limitations

Several limitations have to be considered. First, this is a retrospective observational study with a small population in a single center. Second, echocardiographic parameters (LVDd, LVDs, and LVEF) were used instead of those determined by ECG-gated myocardial perfusion SPECT (EF, EDV, and EDV) to assess LV function, because the precise data of gating were not able to be acquired from all patients because of the frequent ventricular or atrial arrhythmias during the examination. Third, CRTD should have been used in our study population to reduce the occurrence of an ES, it was not available in Japan at that time.

Conclusion

SMTD score assessed by MPS has a strong correlation to the late potentials and higher SMTD score may increase the risk of ES among patients with IDCM and an ICD.

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Irbesartan-mediated AT_1 receptor blockade attenuates hyposmotic-induced enhancement of I_{Ks} current and prevents shortening of action potential duration in atrial myocytes

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Abstract

Introduction: Stretch of the atrial membrane upregulates the slow component of delayed rectifier K^+ current (I_{Ks}). Blockade of angiotensin II subtype 1 receptors (AT_1R) attenuates this increase in I_{Ks}. The present study aimed to examine the effects of irbesartan, a selective AT_1R blocker (ABR), on both the enhancement of I_{Ks} and the shortening of action potential duration (APD) induced by stretching atrial myocytes for exploring the mechanisms underlying the prevention of atrial fibrillation (AF) by ABR.

Methods: Hyposmotic solution (Hypo-S) was used to stretch guinea pig atrial myocytes. I_{Ks} and APD were recorded using the whole-cell patch-clamp technique.

Results: Irbesartan (1–50 μM) attenuated the Hypo-S-induced increase in I_{Ks} and shortening of APD_{90}. Hypo-S increased the I_{Ks} by 113.4%, whereas Hypo-S + 1 μM irbesartan and Hypo-S + 50 μM irbesartan increased the I_{Ks} by only 74.5% and 70.3%, respectively. In addition, Hypo-S shortened the APD_{90} by 19.0%, whereas Hypo-S + 1 μM irbesartan and Hypo-S + 50 μM irbesartan shortened the APD_{90} by 12.1% and 12.0%, respectively.

Conclusion: The actions of irbesartan on electrical changes induced by stretching atrial myocytes are associated with blocking AT_1R. These actions may be beneficial for treating AF.

Keywords

Angiotensin II type 1 receptor, irbesartan, atrial myocytes, I_{Ks}, action potential

Introduction

Increasing evidence suggests that the renin–angiotensin system (RAS) is associated with the occurrence of atrial arrhythmias in experimental animals.[1–5] Recent clinical studies[6–11] have also suggested that blockade of the RAS with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II (Ang II) type 1 receptor (AT_1R) blockers is effective for the treatment of atrial fibrillation (AF). However, mechanisms underlying the treatment are not fully understood, especially concerning actions of the drugs on electrical changes in AF.

The shortening of action potential duration (APD) and effective refractory period (ERP) are generally regarded as pivotal factors for the occurrence of reentry-based AF. During AF, impaired atrial contraction causes the atria to dilate or stretch[12,13] and induce the secretion of Ang II from cardiomyocytes.[14,15] Zankov et al. demonstrated that both exogenous Ang II and hyposmotic-induced membrane stretch potentiates the slow component of delayed rectifier K^+ current (I_{Ks}) in guinea pig myocytes by activating AT_1R, which results in a shortened atrial APD. These results suggest that the shortening of the atrial APD, associated with I_{Ks} enhancement through the activation of AT_1R, plays an important role in facilitating the initiation/maintenance of AF.[16,17] Irbesartan, a selective AT_1R blocker, was reported to

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inhibit heterologously expressed *KCNQ1/KCNE1* (encoding I_{Ks}) channels,[18] which may contribute to its anti-AF mechanism. However, the effective concentrations of the drug for blocking *KCNQ1/KCNE1* channels are far greater than the clinical therapeutic levels achieved in blood.[19,20]

In the present study, we examined the effects of irbesartan on both the increase in I_{Ks} and the shortening of APD induced by hyposmotic solution (Hypo-S) in guinea pig atrial myocytes. The results show that the actions of the drug at therapeutically relevant concentrations on electrical changes induced by the stretching of the atrial cell membrane are, at least partially, associated with blocking AT_1R and therefore beneficial for AF prevention.

Materials and methods

Isolation of guinea pig atrial myocytes

The experimental procedures were conducted in accordance with the guidelines established by the Animal Care and Use Committee of Shiga University of Medical Science (Shiga, Japan). Single atrial myocytes were enzymatically dissociated from the hearts of non-pregnant adult female Hartley guinea pigs (weighing 250–350 g) using a retrograde Langendorff perfusion method as previously described.[16]

Solutions and chemicals

Normal Tyrode solution (140 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 5.5 mM glucose, and 5.0 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH adjusted to 7.4 with NaOH) was used as "isosmotic" extracellular solution (Iso-S, average osmolality: ~285 mOsm/kg). "Hyposmotic" extracellular solution (Hypo-S, average osmolality: ~212 mOsm/kg) was prepared by simply reducing the NaCl concentration to 100 mM in the normal Tyrode solution as previously described.[17] The pipette solution contained 70 mM potassium aspartate, 50 mM KCl, 10 mM KH_2PO_4, 1 mM $MgSO_4$, 3 mM Na_2-ATP (Sigma), 0.1 mM Li_2-GTP (Roche Diagnostics GmbH, Mannheim, Germany), 5 mM ethylene glycol tetraacetic acid (EGTA), and 5 mM HEPES, with the pH adjusted to 7.2 with KOH. Irbesartan (Dainippon Sumitomo Pharma Co., Ltd, Osaka, Japan) was dissolved in dimethyl sulfoxide (DMSO, Sigma) to yield 50 mM stock solution and diluted with Iso-S or Hypo-S to concentrations of 1 and 50 μM, respectively. The concentration of DMSO in the final solution (< 0.1%, *V/V*) slightly increased (< 3.8%) the osmolality of 50 μM irbesartan + Hypo-S (or Iso-S), but had no effect on cell swelling (see Supplementary Materials) or I_{Ks}.

Electrophysiological recordings and data analysis

Single atrial myocytes were either current- or voltage-clamped using the standard whole-cell patch-clamp technique with an EPC-8 patch-clamp amplifier (HEKA Electronics, Lambrecht, Germany). Data were low-pass filtered at 5 kHz, acquired at 2 kHz through a LIH-1600 analogue-to-digital converter (HEKA), and stored on a hard drive using PATCHMASTER software (HEKA). Borosilicate glass electrodes had a tip resistance of 2.5–4.0 MΩ when filled with the pipette solution. All experiments were performed at 36 ± 1°C. I_{Ks} was elicited by depolarizing voltage-clamp steps given from a holding potential of −50 mV to various test potentials, under conditions that the Na^+ current was inactivated by setting the holding potential to −50 mV. The L-type Ca^{2+} channel current ($I_{Ca,L}$) and the rapid component of delayed rectifier K^+ current (I_{Kr}) were blocked by 0.4 μmol/l nisoldipine (Bayer AG, Wuppertal-Elberfeld, Germany) and 0.5 μmol/l dofetilide (Sigma Chemical Co., MO, USA) added to the extracellular solution, respectively.

Variations of I_{Ks} amplitude and the time course of the I_{Ks} were determined by measuring the amplitude of tail currents elicited on repolarization to a holding potential of −50 mV following two seconds (s) of depolarization to +30 mV every 10 s. Voltage-dependence of I_{Ks} activation was evaluated by fitting the *I-V* relation of the tail currents to a Boltzmann equation as follows: $I_{K,tail} = 1/(1+\exp((V_h - V_m)/k))$, where $I_{K,tail}$ is the tail current amplitude, V_h is the voltage at half-maximal activation, V_m is the test potential, and k is the slope factor. The deactivation kinetics of I_{Ks} was determined by fitting a single exponential function to the tail current trace. Cell membrane capacitance (C_m) was calculated on the basis of the capacitive transients during 20 ms voltage-clamp steps (± 5 mV), using the equation $C_m = \tau_C I_0/\Delta V_m(1-I_{ss}/I_0)$, where τ_C is the time constant of the capacitive transient, I_0 is the initial peak current amplitude, I_{ss} is the steady-state current value, and ΔV_m is the amplitude of the voltage step (5 mV).

Action potentials were evoked in current-clamp mode at a rate of 0.2 Hz by suprathreshold current pulses of 2 ms duration applied through the patch electrode. The APD was measured at 90% repolarization (APD_{90}).

All of the averaged data are presented as mean ± S.E.M. with the number of experiments shown in parentheses. Statistical comparisons were evaluated using Student's *t* test or one-way analysis of variance (ANOVA) with Newman-Keuls post-hoc test, as appropriate. A $p < 0.05$ was considered statistically significant.

Results

Irbesartan does not affect the baseline I_{Ks} but attenuates the Hypo-S-induced I_{Ks} enhancement

Based on the concentration-dependent effect of irbesartan on *KCNQ1/KCNE1* channels that was previously reported in a Chinese Hamster Ovary (CHO) expression system,[18] we chose to examine the effects of 1–50 μM irbesartan on I_{Ks}

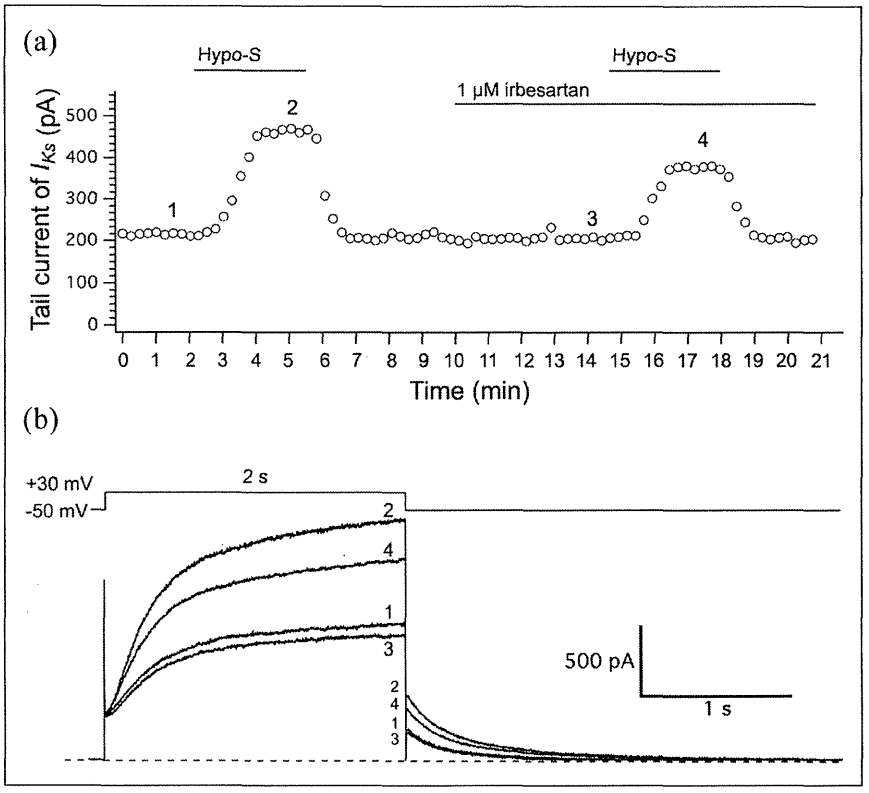

Figure 1. Irbesartan does not affect the baseline I_{Ks} in guinea pig atrial myocytes.
(a) The representative time course of tail I_{Ks} during the first and second (pretreatment with 1 μM irbesartan) exposures to Hypo-S. I_{Ks} was repetitively (every 10 s) activated with 2 s depolarizing step to +30 mV from a holding potential of −50 mV, followed by a repolarization step to −50 mV. Current was determined by measuring and plotting the tail I_{Ks} amplitude. (b) The superimposed I_{Ks} traces recorded before (1) and during first exposure to Hypo-S (2). After washout with normal Tyrode and pretreatment with 1 μM irbesartan for five minutes (3), the same atrial myocyte was exposed to Hypo-S again (4). The dashed line indicates the zero current level. I_{Ks}: delayed rectifier K^+ current.

channels in guinea pig atrial myocytes, since 1–50 μM irbesartan are close to the therapeutic concentrations in blood[19,20] and almost the subthreshold for the inhibition of *KCNQ1/KCNE1* channels. Figure 1(a) depicts a representative time-course of atrial tail I_{Ks} during the first and second exposures to Hypo-S that caused mechanical stretch of the cell membrane and induced enhancement of the I_{Ks}. Before the second exposure to Hypo-S, the myocyte was pretreated with irbesartan for five minutes. We found that 1–50 μM irbesartan did not affect the baseline I_{Ks} of guinea pig atrial myocytes (current traces indicated by 1 and 3 in Figure 1(b)), which was quite similar to that in the CHO expression system.[18] As expected, Hypo-S induced increases in both steady-state and tail I_{Ks} currents (current traces 2 and 4 in Figure 1(b)).

The myocyte swelling observed in Hypo-S reflects the effect of cell membrane stretching that usually occurs during the early stages of AF[12,21] and affects various ion transport mechanisms, including the I_{Ks} enhancement in atrial myocytes.[17,22,23] Figures 2(a) and 2(b) show typical current traces elicited by depolarizing voltage-clamp steps given from a −50 mV holding potential to various test potentials in the absence (panel (a)) or presence of 1 μM irbesartan (panel (b)) while the cells were exposed to Hypo-S. Figure 2(c) summarizes the percentage increases of tail I_{Ks} of cells in Hypo-S in the absence or presence of 1 and 50 μM irbesartan. The percentage increases in tail I_{Ks} for the control cells and those in the presence of 1 and 50 μM irbesartan were 113.40 ± 9.96% (n = 18), 74.52 ± 8.49% (n = 10), and 70.25 ± 9.34% (n = 16), respectively. Increases in tail I_{Ks} in the presence of irbesartan were significantly lower ($p < 0.05$) than those in the control (Figure 2(c)). Figure 2(d) shows the current-voltage relationships for tail I_{Ks} recorded during the superfusion with Iso-S (filled circles), Hypo-S (open circles), or Hypo-S + 1 μM irbesartan (open squares). The voltages for half-activation of tail I_{Ks} (V_h) were obtained by fitting the data to the Boltzmann equation and were 9.06 ± 1.28 mV (n = 22) in Iso-S, 2.08 ± 1.29 mV in Hypo-S (n = 13; $p < 0.01$ vs. Iso-S), and 2.10 ± 1.70 mV in Hypo-S + 1 μM irbesartan (n = 10; $p < 0.05$ vs. Iso-S), respectively. The Hypo-S caused a significant negative shift of V_h; however, irbesartan did not recover this negative shift in the activation gate. In addition, there were no significant differences in the parameters governing gating kinetics, irrespective of irbesartan treatment.

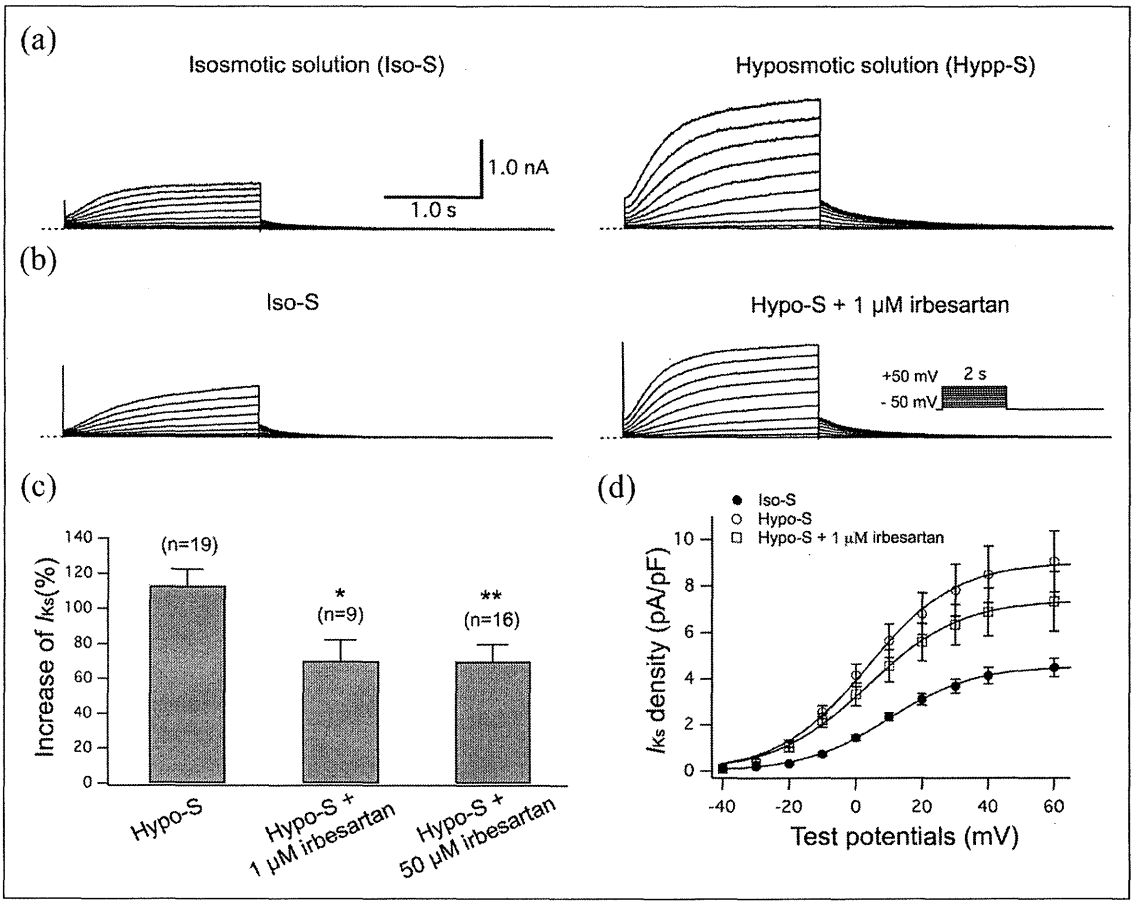

Figure 2. Irbesartan attenuates the Hypo-S-induced increase in I_{Ks} in guinea pig atrial myocytes. The atrial myocytes were initially superfused with control Iso-S followed by Hypo-S in the absence (a) or presence of 1 μM irbesartan (b). I_{Ks} was activated by depolarizing voltage-clamp steps given from a holding potential of −50 mV to potentials listed in the panel (b) inset. The dashed line indicates the zero current level. (c) The percentage increase in tail I_{Ks} amplitudes induced by Hypo-S without and with irbesartan (1 μM and 50 μM) at +30 mV. (d) The *I-V* relations for tail I_{Ks} amplitudes (expressed as current density) recorded during exposure to Iso-S (filled circles), Hypo-S (open circles), or Hypo-S + 1 μM irbesartan (open squares). Smooth curves through the data points denote the least-squares fit with the Boltzmann equation, yielding V_h (see text). *$p < 0.05$ and **$p < 0.01$ vs. Hypo-S. I_{Ks}: delayed rectifier K^+ current.

Table 1 summarizes the effects of 1 μM irbesartan on the deactivation time course of tail I_{Ks} at four different test potentials. The Hypo-S significantly ($p < 0.05$) slowed the deactivation time course of tail I_{Ks} at voltages between −60 mV and −30 mV. There were, however, no significant differences in the increase of τ values (in parentheses) irrespective of irbesartan treatment, though there was a trend in the irbesartan-induced reduction of the Hypo-S effects on I_{Ks} deactivation.

Irbesartan attenuates Hypo-S-induced shortening of the action potential

Figure 3(a–c) shows the superimposed traces of guinea pig atrial action potentials in Iso-S and Hypo-S- (control, Figure 3(a)), Iso-S and Hypo-S + 1μM irbesartan- (Figure 3(b)), and Iso-S and Hypo-S + 50 μM (Figure 3(c)) irbesartan-treated myocytes, respectively. As the bar graphs summarize in Figure 3(d), Hypo-S shortened the APD_{90} by 19.03 ± 1.36 ($n = 17$), whereas Hypo-S + 1 μM irbesartan shortened the APD_{90} by only 12.05 ± 1.38 ($n = 9$; $p < 0.01$ vs. Hypo-S) and Hypo-S + 50 μM irbesartan shortened the APD_{90} by 12.00 ± 1.46 ($n = 14$; $p < 0.01$ vs. Hypo-S). Together, these results suggest that 1–50 μM irbesartan significantly attenuated the Hypo-S-induced shortening of action potentials in atrial myocytes. In addition, no difference in depolarized resting membrane potentials caused by Hypo-S was observed between control cells and those in the presence of irbesartan (data not shown).