TABLE 1
Clinical Characteristics of the 7 Patients

No.	Sex	Clinical Diagnosis	Age of Onset (Days)*	Family History†	QTc (Milliseconds)	Mutations and Polymorphisms
#1	Male	LQTS	0	+	680	N1774D-SCN5A
#2	Male	LQTS	0	–	719	F1486del-SCN5A
#3	Male	LQTS	0	–	638	N406K-SCN5A
#4	Female	BrS	180	+	430	T290fsX53-SCN5A§
#5	Male	LQTS	0	–	506	G628D-KCNH2§
#6	Male	anonymous	19	–	NA	none
#7	Female	LQTS	110	–	604	none
Total	5 Males	4 LQTS,1 BrS	44.1 ± 72.1	2 (29%)	596 ± 109	

*The age when fatal cardiac events were first recorded.
†Family history of sudden cardiac death or aborted sudden cardiac death. §Novel mutations. NA = not available.

of all patients provided written informed consent before the genetic analysis.

Molecular Genetics

Genomic DNA was isolated from peripheral blood lymphocytes. Coding exons of *KCNQ1*, *KCNH2*, *KCNE1–5*, *KCNJ2*, *SCN5A*, and *GJA5* were screened for genetic variants by denaturing high-performance liquid chromatography using a WAVE System Model 3500 (Transgenomic, Omaha, NE, USA). Regarding abnormal conformers, direct sequencing was performed with an ABI PRISM-3130 DNA sequencer (Applied Biosystems, Foster City, CA, USA). In addition to these 10 genes, we also tested *CALM1* gene, which has been reported being involved in young CPVT and LQTS cases.[18,19] The genetic variants identified were probed in a population of 200 ethnically matched controls and in available online databases (http://evs.gs.washington.edu/EVS/and.http://www.ncbi.nlm.nih.gov/projects/SNP/). Variants were numbered by comparison to the reference sequence in the NCBI database (Nucleotide ID *SCN5A* NM_198056.2; *KCNH2* NM_00238.3). To identify the genetic mosaicism in somatic cells, we amplified the target region in genomic DNA and subcloned into TA vectors, then checked the sequence in specific family members.

Mutagenesis and Electrophysiology

The *SCN5A* and *KCNH2* mutant channels were generated by site-directed mutagenesis using the QuickChange-II-XL kit (Stratagene, La Jolla, CA, USA). For *SCN5A*, Chinese hamster ovary (CHO) cells were cultured in a 35-mm dish and transiently transfected with 0.5 μg of either pRcCMV-hH1-wildtype or mutant cDNA in combination with 0.5 μg of the bicistronic plasmid (pEGFP-IRES-hβ1) encoding the enhanced green fluorescent protein and the human β1-subunit (hβ1). For the analysis of I_{Kr}, CHO cells were transfected with 1 μg of either pRcCMV-KCNH2-wildtype or mutant cDNA. Currents were recorded 48–72 h after transfection with the whole-cell patch-clamp technique at 22–23 °C as described elsewhere.[20]

Statistical Analysis

Data are presented as mean ± SD for patients' characteristics, and mean ± SEM for the results of functional assays. Differences between 2 groups were examined using Student's *t*-test. A P value < 0.05 was considered significant.

Results

Clinical Characteristics of the Patient Cohort

Table 1 summarizes the clinical characteristics of the patients included in the analysis. There were 5 males and 2 females with a mean age of onset of 44.1 ± 72.1 days. In 4 patients, cardiac events occurred within 24 hours after birth. Two (29%) patients had a family history of sudden death or aborted cardiac sudden death. Mean QTc interval in patients whose sinus rhythm ECGs were available was 596 ± 109 milliseconds, and 5 patients showed QT prolongation (QTc > 440 milliseconds).

Molecular Genetics

Genetic analyses of LQTS-related genes revealed 4 different *SCN5A* mutations and 1 *KCNH2* mutation in 5 probands in a heterozygous fashion (Table 1 cases #1–5, Fig. 1A). We failed to detect any mutations in cases #6 and #7. N1774D (c. 5319A>G) in *SCN5A* was a missense mutation in exon 28 that replaced asparagine at codon 1774 to aspartic acid, located in the C terminus (Fig. 1B). A deletion of 3 bases in exon 26 caused F1486del (c. 4456_4458delTTC), a deletion of phenylalanine. This mutation lies in the intracellular linker between domain III and IV (Fig. 1B). N406K (c. 1218C > A) was a missense mutation in exon 10 that resulted in the substitution of asparagine in codon 406 to lysine in S6 in domain I (Fig. 1B). T290fsX53 (c. 870delC) was a frame-shift mutation in exon 7. One base pair deletion at c. 870 caused a shift of amino acid sequence resulting in a downstream premature stop of protein translation. The mutation was located in the linker between S5 and S6 in domain I (Fig. 1B). G628D (c. 1883G > A) in *KCNH2* was a missense mutation that replaced glycine with aspartic acid.

Case Summary

A 1-day-old boy with N1774D SCN5A mutation (#1 in Table 1, Fig. 2A)

The patient was first noted to have extreme bradycardia at 27 weeks of gestation. Upon delivery by caesarean section at 38 weeks of gestation, the patient's ECG showed functional

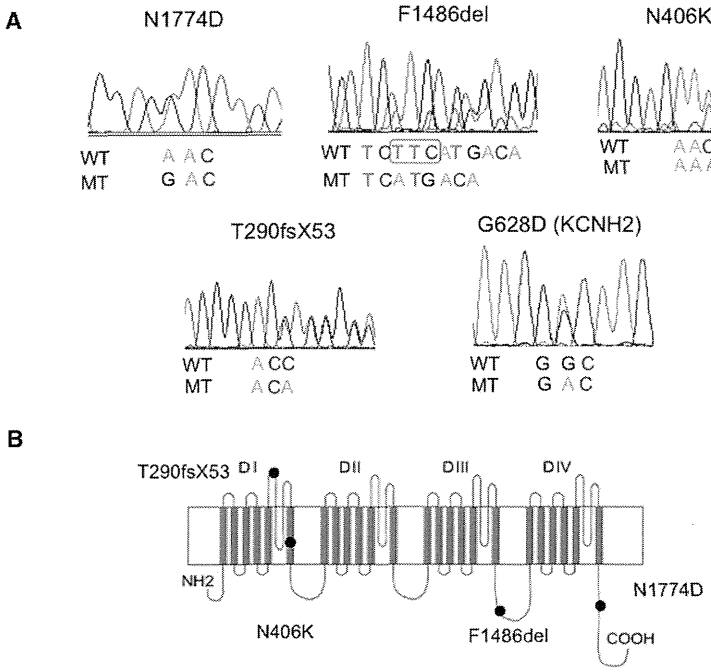

Figure 1. *Molecular diagnoses in 5 probands. Panel (A) shows the original DNA sequences. Panel (B) shows the topology of the voltage gated Na^+ channel and the positions of the 4 variants.*

2:1 atrioventricular block (AV block) due to the prolongation of QTc interval (680 milliseconds) and repetitive TdPs (Fig. 2A left). Intravenous magnesium sulfate and mexiletine, but not lidocaine, were effective at suppressing TdPs. The patient's older brother died suddenly in infancy; however, a genetic sample was not available, and genetic analyses of other individuals in the family failed to identify the mutation. In this family, the sudden death episode of the proband's brother implied the possibility of germ cell mosaicism[21] (Fig. 2A right). However, further analysis of the germ or somatic cell lines of the parents were impossible because additional samples were not available. Thus, we checked the parents' genomic DNAs from lymphocytes by using TA-cloning technique, in the case of having a very small amount of the same mutant allele as the proband. We sequenced total of 50 amplified DNAs for each individual and could not find the same mutation.

A 1-day-old boy with F1486del SCN5A mutation (#2 in Table 1, Fig. 2B)

A male baby was delivered by Caesarean section at 37 weeks of gestation with Apgar score of 4. Prenatal ultrasonography showed the presence of fetal hydrops with AV block, incessant VT, and reduced left ventricular function, suggesting a potential diagnosis of LQTS. Immediately after birth, the patient's ECG showed functional 2:1 AV block (Fig. 2B left) and repetitive TdPs. The QTc interval was extremely prolonged (719 milliseconds) with late-appearing bizarre T waves. Intravenous amiodarone, but not lidocaine and magnesium sulfate, temporarily suppressed TdPs, which eventually became intractable, and the patient died 18 hours after birth. Genetic analyses in the patient's parents failed to detect the same mutation, suggesting that it was de novo mutation (Fig. 2B, right). We previously reported the clinical information of this case.[22]

A 1-day-old boy with N406K SCN5A mutation (#3 in Table 1, Fig. 2C).

The patient was a 1-day-old male baby who developed TdP in the incubator shortly after birth. ECG showed that the QTc interval was significantly prolonged (638 milliseconds, Fig. 2C left). The patient was treated by intravenous lidocaine, and oral administration of mexiletine and propranolol. The QTc interval shortened to 478 milliseconds after 8 months, and a second TdP attack never occurred. This *SCN5A* variant was not found in the patient's parents, suggesting a de novo origin (Fig. 2C right).

A 6-month-old girl with T290fsX53 SCN5A mutation (#4 in Table 1, Fig. 2D)

A female baby was delivered after full and normal gestation and developed repetitive syncope due to VT at 6 months of age. The patient's VT was successfully controlled by intravenous magnesium sulfate. However, this patient developed VT again at 4 years of age, and rest-ECG recorded at that time showed an incomplete right bundle branch block with J-point and ST segment elevations in the right precordial leads (Fig. 2D). The patient's 34-year-old father also suffered from repetitive syncope due to VT and underwent an implantable cardioverter-defibrillator implantation. The genetic tests revealed that her father and younger brother also had the same *SCN5A* mutation in a heterozygous condition (Fig. 2D pedigree).

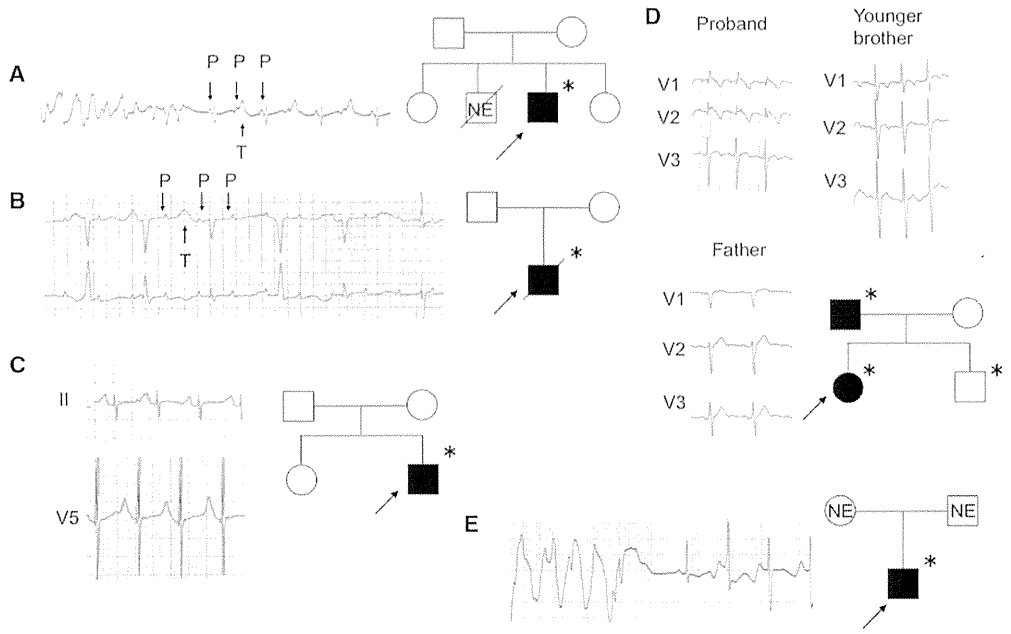

Figure 2. *Pedigrees and ECGs of cases #1–5. In pedigrees, closed symbols indicate members affected by clinical phenotypes. Asterisks indicate mutation-positive cases. (A) Case #1, 1-day-old boy with N1774D SCN5A mutation. (Left) Monitoring ECG shows a short run of TdP and subsequent 2:1 AV block. (Right) Pedigree. NE = not examined. (B) Case #2, 1-day-old boy with F1486del SCN5A mutation. (Left) Baseline ECG showing significantly prolonged QT interval and consequent 2:1 AV block. (Right) Pedigree. (C) Case #3, 1-day-old boy with N406K SCN5A mutation. (Left) Baseline ECG showing prolonged QTc interval (638 milliseconds). (Right) Pedigree. (D) Case #4, 6-month-old girl with T290fsX53 SCN5A mutation. (Upper and lower left panels) Baseline ECGs of the proband at 4 years of age, and the proband's father and younger brother. Only proband's ECG shows the coved-type ST elevation in right precordial leads. (Lower right panel) Pedigree. (E) Case #5, 1-day-old boy with G628D KCNH2 mutation. (Left) Monitoring ECG of TdP. (Right) Pedigree. NE = not examined.*

TABLE 2

Biophysical Parameters of SCN5A-WT and Mutant Channels

	WT	N1774D	F1486del	N406K	T290fsX53
	N = 19	N = 13	N = 12	N = 11	N = 16
Peak density (pA/pF)	–435.2 ± 62.2	–941.0 ± 75.2[b]	–202.9 ± 78.2[b]	–91.9 ± 81.7[b]	– 28.4 ± 67.8[b]
Steady-state activation	N = 18	N = 13	N = 11	N = 11	–
V1/2	–54.4 ± 2.1	–62.3 ± 2.5[a]	–63.3 ± 2.7[a]	–45.8 ± 2.7[a]	–
K	4.4 ± 0.5	4.2 ± 0.6	2.7 ± 0.6[a]	7.2 ± 0.6[b]	–
Steady-state inactivation	N = 21	N = 16	N = 16	N = 13	–
V1/2	–83.8 ± 2. 1	–84.7 ± 2.4	–58.4 ± 2.4[b]	–80.9 ± 2.6	–
K	–5.7 ± 0.2	–5.4 ± 0.2	–5.0 ± 0.2	–5.5 ± 0.3	–
Current decay at -30 mV	N = 18	N = 14	N = 12	N = 10	–
τf	0.6 ± 0.1	1.0 ± 0.1[b]	1.5 ± 0.3[b]	1.3 ± 0.1[b]	–
τs	3.2 ± 0.4	8.7 ± 1.9[a]	38.7 ± 7.6[a]	4.3 ± 1.0	–
Late Na^+ current	N = 12	N = 13	N = 10	N = 6	–
% of Peak	1.0 ± 0.3	1.7 ± 0.2[a]	12.3 ± 1.9[b]	5.5 ± 1.3[a]	–
Recovery from inactivation	N = 18	N = 12	N = 10	N = 11	–
Half recovery time	2.8 ± 1.6	1.4 ± 0.3	55.4 ± 12.3[b]	1.6 ± 0.3	–

Compared to that of the WT.
[a]$P < 0.05$, [b]$P < 0.01$.

A 1-day-old boy with G628D KCNH2 mutation (#5 in Table 1, Fig. 2E)

The proband was first pointed out VT at 30 weeks of gestation. After full-term vaginal delivery, the patient had recurrent TdPs with prolonged QT interval (506 milliseconds, Fig. 2E left) on day 1, which required multiple cardioversions. Administration of magnesium sulfate, mexiletine, and a β-blocker was effective. The patient's family members did not provide consent for genetic testing (Fig. 2E, right).

Functional Assay

To clarify the genotype–phenotype correlation, we performed a functional assay using a heterologous expression system in CHO cells. Numerical data are summarized in Tables 2 and 3. Figure 3A shows representative whole-cell current traces from cells expressing *SCN5A*-wild type (WT), N1774D, F1486del, N406K, and T290fsX53. Three of the mutant sodium channels except T290fsX53 were functionally well expressed. The peak current density was

TABLE 3
Biophysical Parameters of KCNH2-WT and G628D Mutant Channels

	WT 1.0 μg	WT 0.5 μg	WT 0.5 μg/G628D 0.5 μg	G628D 0.5 μg
Peak tail current density (pA/pF)	25.5 ± 2.5	17.3 ± 3.6	14.4 ± 3.0[a]	2.1 ± 2.6[b]
Activation V1/2	–9.3 ± 2.7	–	–9.9 ± 3.0	–
Activation K	9.8 ± 0.5	–	11.7 ± 1.5	–

Compared to that of WT 1.0 μg, [a]$P < 0.05$, [b]$P < 0.01$.

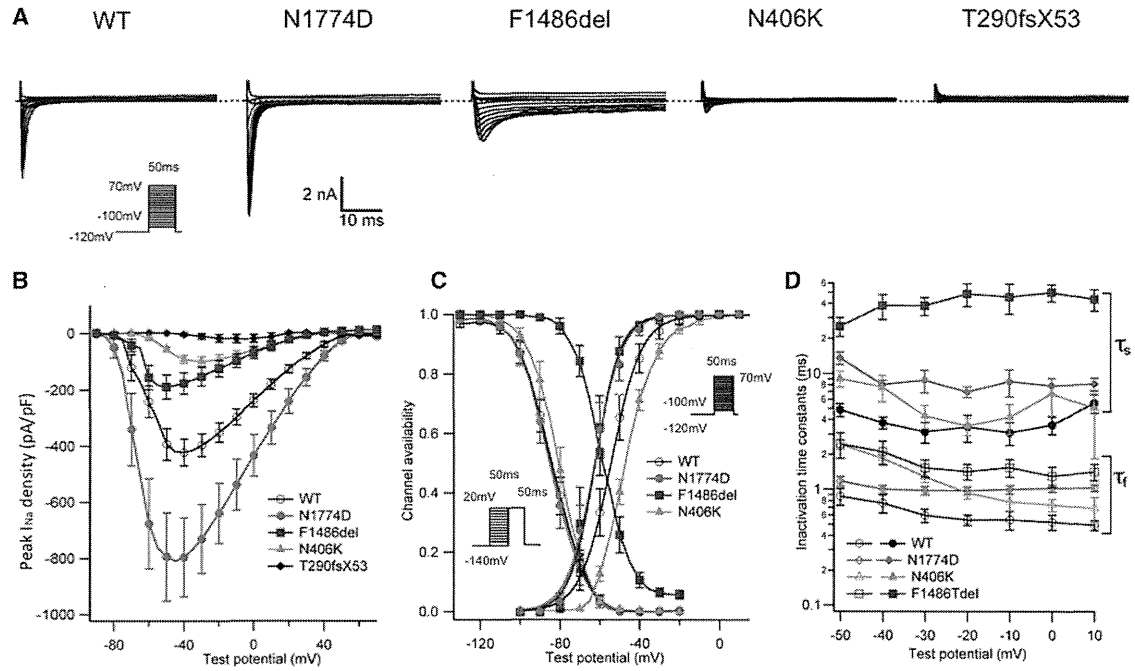

Figure 3. *Functional assay of SCN5A mutation channels. (A) Whole-cell current recordings of WT, N1774D, F1486del, N406K, and T290fsX53mutant Na^+ channels. Currents were recorded at various membrane potentials from −100 to 70 mV in 5mV increments from a holding potential (−120 mV). (B) Current–voltage relationship. Current was normalized to cell capacitance to give a measure of Na^+ current density. (C) Voltage dependence of steady-state inactivation and activation of WT, N1774D, F1486del, and N406K mutant channels, measured using standard pulse protocols as shown in insets. The currents of the T290fsX53 mutant channels were too small to draw these curves. Curves were fit with the Boltzmann equation: $I/Imax = -1/\{1 + exp[(V - V_{1/2})/k]\} + C$. (D) Time constants for the voltage dependence of inactivation in WT, N1774D, F1486del, and N406K mutant channels. Open symbols indicate the fast component of the time constant (τ_f), and closed symbols indicate the slow component (τ_s).*

significantly larger in N1774D than in WT channels, but it was smaller in the F1486del and N406K mutant channels. T290fsX53 channels showed no measurable inward Na^+ currents. These differences in current densities are also obvious in Table 2 and Figure 3B, which shows the peak current density-voltage relationship for 5 different conditions of transfection.

Figure 3C shows conductance–voltage and steady-state inactivation curves for the WT and 3 mutant sodium channels. Regarding steady-state activation, the half-maximal potentials of N1774D channels and F1486del were negatively shifted (~ −8 mV) compared with that of WT, whereas that of N406K was shifted positively (~ +9 mV) (Table 2). With respect to steady-state inactivation, N1774D and N406K channels did not differ from WT channels, whereas F1486del channels exhibited a significantly positive shift (~ +25 mV, Table 2).

The inactivation time course for WT and mutant channel currents was fitted by double exponentials, which yielded fast and slow components of time constants (τ_f and τ_s). Time constants thus measured were plotted as a function of various test potentials from a holding voltage of –120 mV (Fig. 3D). Both τ_f and τ_s were significantly larger in N1774D and F1486del mutant channels at test potentials positive to –30 mV, indicating that these mutations cause a significantly slower Na^+ current decay than that of the WT. The N406K mutant channels showed larger τ_f, but not τ_s.

Figure 4A shows 4 representative sets of current traces recorded following a protocol indicated in the inset in the absence and presence of tetrodotoxin (30 μM). Depolarization pulses were applied every 5 seconds. Residual and persistent tetrodotoxin-sensitive components were measured at the end of the depolarization pulse in multiple cells, and their mean values against peak currents were expressed as bar graphs in

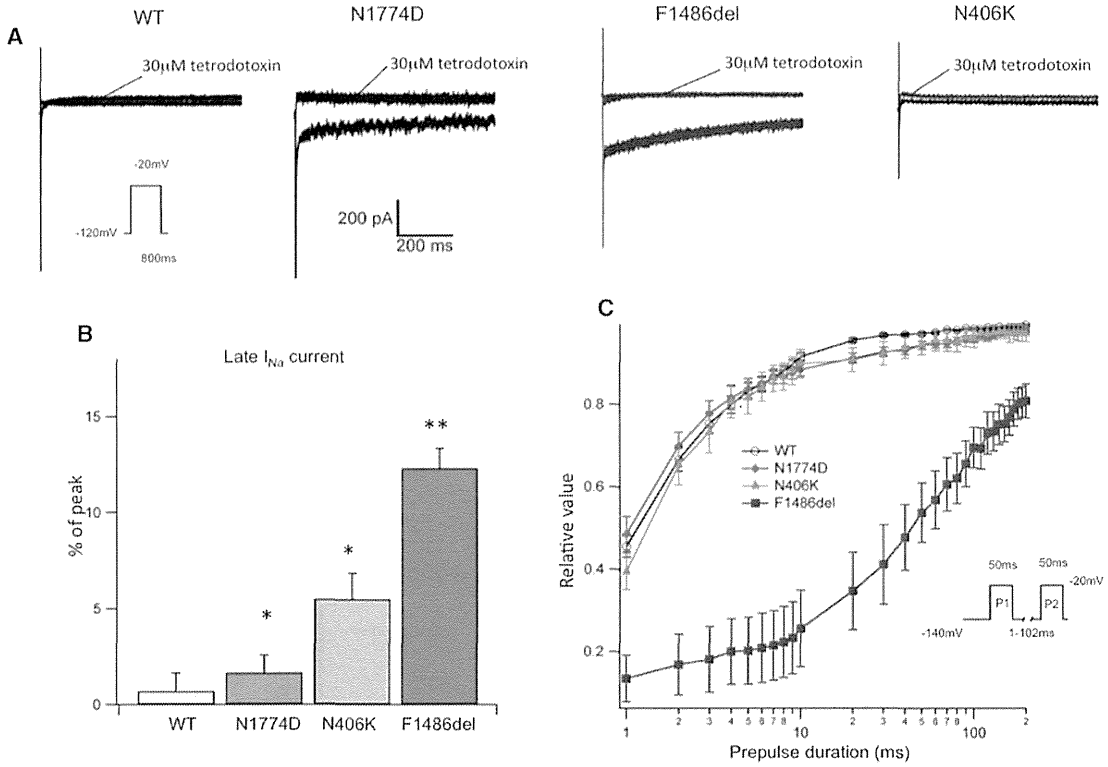

Figure 4. *Late component of inward Na^+ currents and recovery. (A) Tetrodotoxin sensitive late Na^+ currents of WT, N1774D, F1486del, and N406K mutant channels. Depolarization pulses were applied every 5 seconds. (B) The proportion of late Na^+ currents to peak density. N1774D, F1486del, and N406K mutant channels showed significantly higher late Na^+ currents than the WT. Because of its small peak current density, the proportion of the late component of N406K channels was very high, despite its appearance in the original trace (Fig. 4A). *$P < 0.05$, **$P < 0.01$. (C) Recovery from inactivation. Peak inward currents of the second pulse recorded using the double-pulse method were normalized to the first one and plotted against the recovery time on a logarithmic axis.*

Figure 4B. F1486del, N1774D, and N406K channels carried significantly larger late components of Na^+ currents than the WT. Recovery from the inactivation state was assessed using a double-pulse method (Fig. 4C inset). After the initial depolarization, the second test pulse was applied to the same potential at various intervals, and the ratio of the peak inward current on the second pulse to that of the first one was plotted as a function of the interval between them. The half recovery time of the F1486del mutant channel was significantly longer than that of the WT, whereas N1774D and N406K mutant channels showed no major changes (Fig. 4C, Table 2). Functional alternations induced by F1486del were consistent with those previously reported.[23] In case #1 and #2, lidocaine failed to suppress TdP, although mexiletine suppressed that of case #1. Therefore, we tested the effects of these class Ib drugs on the late I_{Na} of the N1774D channels, and also that of lidocaine on the late I_{Na} of the F1486del channels. Both lidocaine and mexiletine at 10μM partly suppressed the late I_{Na} of the N1774D channels (lidocaine 35.0 $\pm$ 6.6%, mexiletine 52.6 $\pm$ 5.9%), and there was no significant difference between the effects of these 2 agents. Lidocaine also suppressed the late I_{Na} of the F1486del channels (49.5 $\pm$ 6.3% at 10μM, 63.7 $\pm$ 13.8% at 50μM, data not shown). Thus, we failed to demonstrate the ineffectiveness of lidocaine on both cases #1 and #2, and the different effect of mexiletine on case #1.

Figure 5A shows representative current traces from cells transfected with *KCNH2*-WT, *KCNH2*-WT/G628D, and *KCNH2*-G628D. Cells transfected with G628D 1.0 μg showed almost no tail currents (Fig. 5A, right), and cells cotransfected with WT 0.5 μg and G628D 0.5 μg showed significantly smaller tail currents than cells transfected with WT 1.0 μg (Fig. 5A, left and middle). On the other hand, no significant difference in tail current densities was detected between cells cotransfected with WT 0.5 μg/G628D 0.5 μg and WT 0.5 μg alone (Fig. 5B, Table 3). The normalized tail currents and voltage relationship were not altered by coexpression of G628D (Fig. 5C, Table3).

Discussion

In this study, we analyzed 7 babies with clinical records showing potentially fatal arrhythmias, and 5 of them were found to have rare genetic variants in ion channel genes, namely 4 mutations in *SCN5A* and 1 in *KCNH2*. Three of the 4 *SCN5A* mutations showed late I_{Na} associated with LQT3, whereas a frameshift mutation caused a total loss of channel function. *KCNH2* mutation channels showed loss-of-function features associated with LQT2.

The relationship between ventricular tachyarrhythmia in early childhood and inherited arrhythmia syndromes has been discussed for decades. In 1976, Schwartz *et al.* first suggested

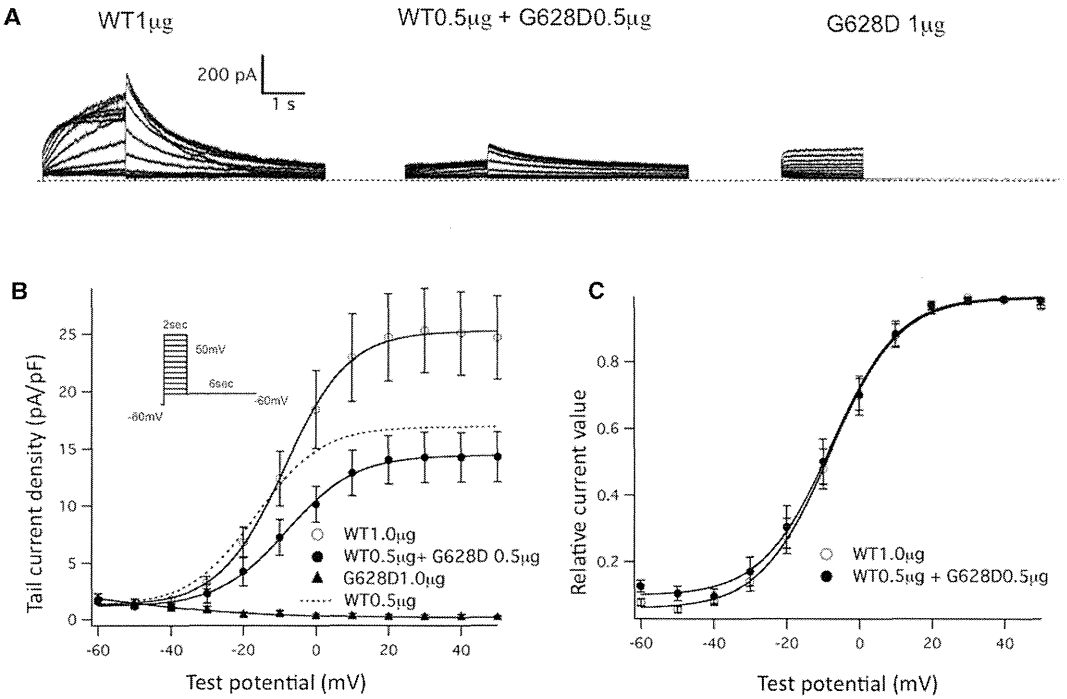

Figure 5. *Functional assay of KCNH2 WT and G628D mutant channels. (A) Original traces from cells transfected with WT 1.0 μg, WT 0.5 μg + G628D 0.5 μg, and G628D 1.0 μg recorded using step pulse protocol from −60 mV to 50 mV as shown in the inset of Figure 5B. Cells transfected with G628D 1.0 μg showed no measurable tail current. (B) Tail current voltage relationship of 4 different conditions of transfection: WT1.0 μg, WT 0.5 μg, WT 0.5 μg + G628D 0.5 μg, and G628D 1.0 μg. (C) Voltage dependence of the tail current normalized to peak current densities. Data are fit by double exponential. Open circles indicate cells transfected with WT1.0 μg, closed circles, WT 0.5 μg + G628D 0.5 μg.*

an association between SIDS and cardiac channelopathies.[5] These authors surveyed the ECGs of 34,442 newborns and found that babies with prolonged QTc had a high prevalence of SIDS.[24] Later studies showed that approximately 9% of SIDS victims had genetic mutations in cardiac ion channel genes, especially in sodium current related genes.[9-15] Therefore, certain proportion of SIDS can be attributed to cardiac channelopathies and fatal arrhythmia attacks.

However, the prevalence of cardiac channelopathies in infantile fatal arrhythmia cases and the indications for genetic screening remain unresolved issues. Existing reports on SIDS victims have been based on postmortem analyses; therefore, information about clinical events has not been available. In a study by Kanter *et al.*,[25] genetic screening of ventricular tachyarrhythmia or conduction abnormality cases < 2 years of age showed that 5 of 5 (100%) cases had mutations in either *SCN5A*, *CACNB2b*, or *KCNH2*. The authors concluded that infantile fatal ventricular arrhythmias without structural cardiac disease are strong predictor of cardiac channelopathies.

In this study, we also showed a high prevalence of channelopathies, and as previously reported,[5,6] a significant dominance of *SCN5A* mutations. In 2010, we reported the results of a nationwide survey on LQTS in the fetal, neonatal, and infantile periods.[26] In contrast to our present results, in that study, more than 70% of genotyped cases were carriers of either *KCNQ1* or *KCNH2* mutations. This may reflect the different characteristics of the 2 cohorts, as the previous survey included both symptomatic and asymptomatic patients, indicating that *SCN5A* mutations are more common in babies with documented fatal arrhythmias.

Functional assays in cells expressing N1774D and F1486del showed larger window currents and larger late I_{Na}. Especially, as previously reported,[23] the F1486del channel showed a massive positive shift of the inactivation curve. These gain-of-function features are reasonable considering the LQT3 phenotype. In particular, the extremely large late I_{Na} of the F1486del channel corresponded well with the severity of case #2.[22] F1486 is located in the intracellular loop between domains III and IV of Nav1.5, which plays an important role in channel inactivation. A 3-residue hydrophobic motif (IFM: 1485I-1486F-1487M) is a key structure in this region and the F1486del mutation resulted in the disruption of the motif.

The N406K channels showed smaller peak I_{Na} densities and smaller window currents, and the T290fsX53 channels showed no measurable I_{Na}. These loss-of-sodium channel function features are generally associated with BrS in adults. However, Chockalingam *et al.* reported that in young children, Brugada-type ST elevation is not a major ECG finding of loss-of-function sodium channelopathies.[27] Reports about cases of infants with loss-of-sodium channel function without typical coved-type ECGs support their findings.[28-32] Indeed in our present study, case #3, carrying the N406K mutation, and the younger brother of case #4, carrying the T290fsX53 mutation, did not show Brugada-type ST elevation, whereas case #4 showed typical type 1 Brugada ECG. In addition to

these findings, the N406K channel showed large late I_{Na} as well, which is supposed to be responsible for the expression of LQTS phenotype in case #3.

Conclusion

Genetic screening of 7 patients with infantile fatal arrhythmias showed a high prevalence of cardiac ion channel mutations, which suggests that physicians should consider genetic screening in the case of infantile fatal arrhythmia. Of the 5 mutations detected, 4 were *SCN5A* mutations. This result was in agreement with those of previous reported postmortem analyses of SIDS victims. A functional assay showed both gain- and loss-of-function changes in channel kinetics in *SCN5A* mutations and loss of channel function in *KCNH2* mutation.

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Circadian pattern of fibrillatory events in non–Brugada-type idiopathic ventricular fibrillation with a focus on J waves

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BACKGROUND The circadian pattern of ventricular fibrillation (VF) episodes in patients with idiopathic ventricular fibrillation (IVF) is poorly understood.

OBJECTIVE The purpose of this study was to assess the circadian pattern of VF occurrence in patients with IVF.

METHODS Excluding Brugada syndrome and other primary electrical diseases, the circadian pattern of VF occurrence was determined in 64 patients with IVF. The clinical and electrocardiographic characteristics were compared among patients with nocturnal (midnight to 6:00 AM) VF and nonnocturnal VF in relation to J waves. A J wave was defined as either notching or a slur at the QRS terminal >0.1 mV above the isoelectric line in contiguous leads.

RESULTS The overall distribution pattern of VF occurrence showed 2 peaks at approximately 6:00 AM and around 8:00 PM. Nocturnal VF was observed in 20 patients (31.3%), and J waves were present in 14 of these 20 individuals (70.0%), whereas J waves were less frequent in the 44 nonnocturnal patients with VF: 16 (36.4%) ($P = .0117$). Among patients with J waves, nocturnal VF was observed in 46.7% with a peak at approximately 4:00 AM. Nocturnal VF was less common in patients without J waves, occurring in only 17.6% ($P = .0124$). Both the type and location of J waves and the pattern of the ST segment were similar between the nocturnal and nonnocturnal VF groups. J waves were associated with a VF storm and long-term arrhythmia recurrence.

CONCLUSION In IVF, the presence of J waves may characterize a higher nocturnal incidence of VF and a higher acute and chronic risk of recurrence.

KEYWORDS Idiopathic ventricular fibrillation; Circadian rhythm; J waves; Ventricular fibrillation; Sudden cardiac death

ABBREVIATIONS **BS** = Brugada syndrome; **ECG** = electrocardiogram/electrocardiographic; **ICD** = implantable cardioverter-defibrillator; **IVF** = idiopathic ventricular fibrillation; **VF** = ventricular fibrillation

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Introduction

In approximately 5%–12% of cases of sudden cardiac death, ventricular fibrillation (VF) has been shown to occur without structural heart disease and in the absence of any known reason.[1,2] Among VF occurring in the heart without demonstrable heart disease, Brugada syndrome (BS) is characterized by a unique electrocardiogram (ECG) profile in J/ST/T waves,[3] whereas other idiopathic ventricular fibrillation (IVF) conditions may feature an ECG showing only terminal QRS abnormalities, called J waves.[4,5] Case studies confirmed an association between J waves and the incidence of VF or sudden cardiac death.[6–8] However, a substantial number of patients with IVF may demonstrate no specific ECG signs.[6,9] Many features of BS have been extensively examined, but those of non–BS-type IVF, both with and without J waves, are less well understood.

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The characterization of patients with IVF in relation to the timing of VF occurrence may be important from the perspective of both risk stratification and determining acute and long-term disease management.

We reanalyzed our case-control study of patients with IVF with and without J waves,[9,10] focusing on the relationship between the circadian patterns of distribution of VF events, with respect to the time of the day these events occurred and to the presence of J waves.

Methods

Patients

Patients with IVF included in this study met the following inclusion criteria: documentation of VF at the time of cardiac arrest; absence of structural heart disease and presence of normal cardiac function; negative serology for inflammatory diseases and absence of electrolyte imbalances; absence of coronary artery disease; and negative provocative test for coronary spasms. Normal complete blood cell counts and serum chemistry were verified by blood work. Primary electrical diseases, such as BS,[3] long[11] or short[12] QT interval, and Wolff-Parkinson-White syndrome, were also excluded as were patients with IVF who showed a right bundle branch block.[13] BS was diagnosed on the basis of characteristic ECG signs, with or without provocation by pilsicainide.[14] Structural heart diseases were excluded by ECG, echocardiography, and cardiac catheterization. Coronary spasm was excluded by a provocation test using either acetylcholine or ergonovine maleate.[15] Induction of VF was attempted giving 1–2 ventricular extrastimuli to the refractory period at paced cycle lengths of 600 and 400 ms, from the apex and then the outflow tract of the right ventricle. An implantable cardioverter-defibrillator (ICD) was placed after informed consent was obtained from patients.

This study was approved by the ethics committee of the Niigata University School of Medicine.[9,10]

ECG analysis

Twelve-lead ECGs were recorded on admission, and patients were placed on ECG monitoring for at least 1 week. ECGs were recorded either daily or every other day, and they were also recorded both before and after patients underwent catheterization and ICD implantation procedures.

In this study, J waves were diagnosed by the following criteria: (1) a notch or slur in the terminal portion of the QRS complex and (2) amplitude >0.1 mV above the isoelectric line in at least 2 contiguous leads.[6,9,10,16] When J waves were present, the type of J wave (notch or slurring), the distribution, and the pattern of the ST segment following the J wave were evaluated.[17,18] In addition, ECGs were analyzed for abnormalities in the RR, PR, and QT intervals, and the QT interval was corrected by using Bazett's formula. ECGs were read by 2 cardiologists. When there was disagreement on J waves, they discussed the results together to reach agreement.

Data analysis

The circadian patterns of VF occurrence were obtained by plotting the number of cases of the first VF episode against the corresponding time of the day, and the clinical and ECG characteristics were compared among patients with VF occurring during the nocturnal period (midnight to 6:00 AM).[19,20] The patterns of VF occurring at other times—midnight to 8:00 AM, 10:00 PM to 6:00 AM, and 10:00 PM to 8:00 AM—were also analyzed as were those occurring at night. The activity of the patient at the time of VF occurrence was reviewed.

The characteristics of J waves and the pattern of the ST segment—horizontal/descending or rapidly ascending/upsloping according to predefined criteria[17,18]—were compared between patients with nocturnal VF and those with nonnocturnal VF. Finally, the clinical and ECG characteristics were compared on the basis of the presence of J waves.

Statistical analyses

The continuous data are presented as mean ± SD, and the categorical data are presented as absolute numbers and percentages. The statistical comparisons among the groups were made using a t test or analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables. The statistical analyses were performed with SPSS, version 12.0 (SPSS Inc, Chicago, IL). A 2-sided P value of $<.05$ was considered statistically significant.

Results

Patients' characteristics

Sixty-four patients for whom the time of VF occurrence was available met the inclusion criteria for IVF. The first VF episode occurred outside the hospital in all patients and was successfully defibrillated by an emergency team before admission to the hospital.

A family history of sudden cardiac death was noted in 7 of 64 patients (10.9%). VF presented as an electrical storm in 14 patients (21.9%), which occurred in 1–2 hours after admission. VF was induced by ventricular programmed stimulation in 43 patients (67.2%) (Table 1). J waves were observed in 30 patients (46.9%) on the day of admission and showed variable changes thereafter (Figure 1, Table 2). When patients presented to the hospital without J waves, none developed new J waves during the remainder of their hospitalization.

Circadian pattern of VF occurrence

The overall distribution pattern of VF occurrence in the study's 64 patients showed the following 2 peaks: at approximately 6:00 AM and around 8:00 PM (Figure 2). During the nocturnal period (midnight to 6:00 AM), VF occurred in 20 of 64 (31.3%) patients with IVF. There was no difference in either the clinical or ECG findings, except for the QT and corrected QT intervals, which were shorter in patients with nocturnal VF (Table 1).

In the 30 patients with J waves, 46.7% of VF occurred during the nocturnal period, whereas only 17.6% of VF occurred during the same period in the 34 patients without J

Table 1 Clinical and ECG characteristics of patients with IVF who had nocturnal or nonnocturnal VF

Characteristic	All patients (n = 64)	Patients with nocturnal VF (n = 20)	Patients with nonnocturnal VF (n = 44)	*P*
Age (y)	45.2 ± 12.0	45.2 ± 12.0	39.8 ± 18.5	.2500
Sex: male	58 (90.6)	18 (90.0)	40 (90.9)	.9084
FH of SCD	7 (10.9)	3 (15.0)	4 (9.1)	.4929
VF induction	43 (67.2)	15 (75.0)	28 (63.4)	.8979
ES	14 (21.9)	5 (25.0)	9 (20.5)	.6860
ECG parameters				
RR interval (ms)	927 ± 155	901 ± 154	939 ± 177	.4720
PR interval (ms)	169 ± 34	172 ± 38	166 ± 30	.5913
QRS duration (ms)	98 ± 14	98 ± 15	98 ± 14	.8843
QT interval, (ms)	385 ± 26	373 ± 27	391 ± 26	.0319
QTc interval ($ms^{1/2}$)	402 ± 32	386 ± 31	409 ± 34	.0207
J waves	33 (51.6)	14/20 (70.0)	16/44 (36.4)	.0117
J-wave amplitude* (mV)	0.32 ± 0.15	0.32 ± 0.15	0.30 ± 0.15	.7587
Notch type	14/33 (42.4)	9/17 (52.9)	5/16 (31.3)	.2053
Horizontal/downward ST segment	13/33 (39.4)	8/17 (47.1)	5/16 (31.3)	.3513

Values are presented as mean ± SD or as n (%).

ECG = electrocardiogram; ES = electrical storm; FH = family history; IVF = idiopathic ventricular fibrillation; QTc = corrected QT; SCD = sudden cardiac death; VF = ventricular fibrillation.

*From patients with J waves.

waves ($P = .0124$; Table 2). Patients with J waves showed a peak of VF occurrence at approximately 4:00 AM (Figure 2). VF occurred in 50.0% and 20.6% of patients with IVF with and without J waves, respectively, during night hours (10:00 PM to 6:00 AM) ($P = .0064$; Table 2).

VF occurred during other "nocturnal" time periods more often in patients with J waves compared with those without J waves: 60.0% vs 20.6% ($P = .0011$) for midnight to 8:00 AM, or 66.7% vs 23.5% ($P = .0004$) for 10:00 PM to 8:00 AM.

Among patients with VF occurred during the second peak (between 6:00 PM and 10:00 PM), 3 patients (4.7%) were with J waves and 13 patients (20.3%) were without J waves, and they were awake when VF occurred. Nocturnal VFs occurred after the patients went to bed before midnight or before they woke up. There was no nighttime worker, and intense physical and emotional activities were denied. In contrast, VFs occurring in other times of the day developed on the way to the office or school or during performance of everyday work. One farmer had VF outside during daytime, and another student had VF during jogging around 9:00 PM. The 2 patients had no J waves, and VF was unrelated to intense physical exercise or emotional stress.

J waves and VF occurrence

The prevalence of J waves was higher in patients with nocturnal VF (14 of 20 [70.0%]) than in patients with nonnocturnal VF (16 of 44 [36.4%]) ($P < .0117$; Table 1).

A VF storm (≥3 episodes within a day) occurred in 43.3% of patients with J waves and in 2.9% of patients without J waves ($P < .0001$; Table 2). The notch-type J wave was observed in 9 of 14 patients (64.3%) with nocturnal VF vs 5 of 16 (31.2%) patients with nonnocturnal VF ($P = .0704$). A horizontal or downward ST segment was observed in 5 of 14 (35.7%) patients with nocturnal VF vs 5 of 16 (31.3%) patients with nonnocturnal VF ($P = .7958$).

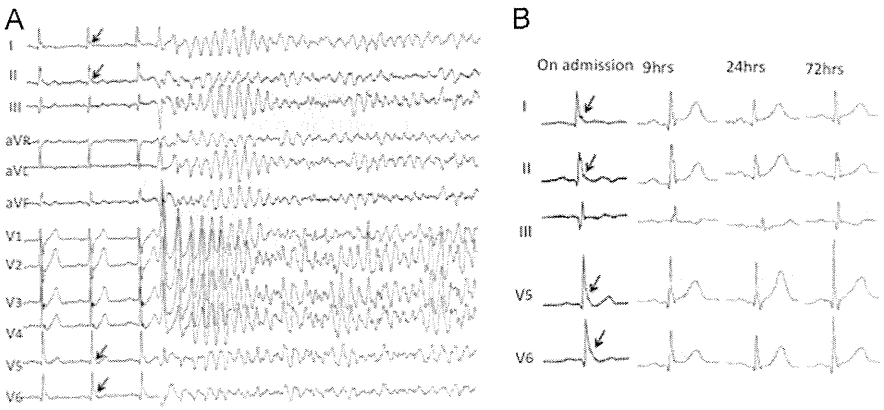

Figure 1 ECG and serial changes of J waves after admission. The patient was a 44-year-old man who experienced cardiac arrest at his home at approximately 4:00 AM. VF was defibrillated by emergency medical personnel. VF recurred after admission (**A**). His ECG showed J waves in the inferior and lateral precordial leads (arrows). J waves decreased spontaneously in amplitude, and only ST-segment elevation <0.1 mV was observed in leads I, V_5, and V_6 at 72 hours (**B**). ECG = electrocardiogram; VF = ventricular fibrillation.

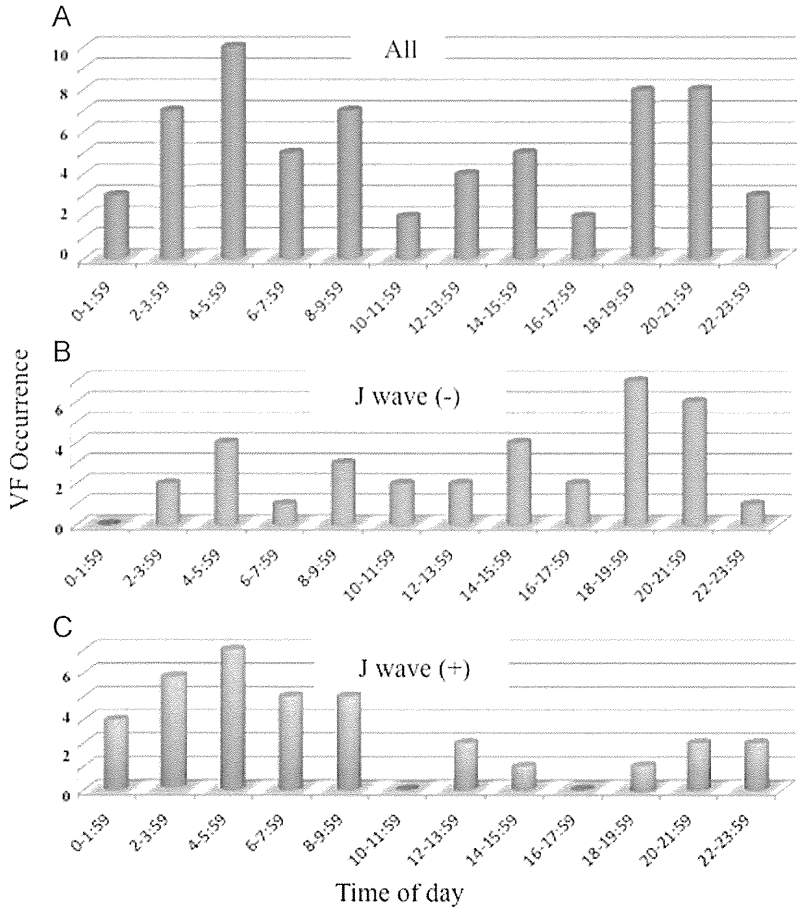

Figure 2 Distribution patterns of VF occurrence. **A:** In the overall population, the following 2 peaks are evident: at approximately 6:00 AM and 8:00 PM. VF occurred during the nocturnal period (midnight to 6:00 AM) in 31.3%. **B:** Patients without J waves showed a small peak in the morning and a larger one in the late evening. **C:** Patients with J waves showed a peak in VF events in the early morning but no peak during the daytime. The incidence of VF occurring during the nocturnal period (midnight to 6:00 AM) was significantly higher in patients with J waves than in those without J waves: 46.7% vs 17.6% ($P = .0117$). VF = ventricular fibrillation.

Outcomes

VF storms were most effectively controlled by the intravenous administration of isoproterenol, and J waves were attenuated by isoproterenol as reported earlier.[9] Among patients with VF storms, all except for one patient had J waves (Table 2). One patient with J waves and another without J waves underwent surgery. Frequent VF-triggering premature ventricular beats were mapped and ablated by cryosurgery. One patient without J waves underwent RF catheter ablation for VF-triggering premature ventricular beats.

During hospitalization, 4 patients died of VF before ICD implantation: 3 of these patients had J waves and 1 patient did not, all due to uncontrolled VF. Thirteen patients—4 with J waves and 9 without J waves—refused ICD implantation and were followed without an ICD. The remaining patients underwent ICD implantation. In 1 patient without J waves, the ICD generator was explanted at the time of exchange, 7 years later. The following antiarrhythmic drugs were prescribed to a limited number of patients with J waves on the basis of the judgment of their physicians: quinidine (n = 2), disopyramide (n = 3), bepridil (n = 3), or orciprenaline (n = 1). All those patients were under ICD therapy. Of 13 patients refusing ICD, 4 with J waves and 2 without J waves were treated with antiarrhythmic drugs while the remainder were followed without medications.

During the follow-up period of 7.4 ± 3.2 years, VF recurred in 6 of 27 patients with J waves (22.2%). The timings of VF occurrence were nocturnal to nocturnal in 2 patients, nonnocturnal to nocturnal in 2 patients, and nonnocturnal to nonnocturnal in 2 patients. One of 33 patients without J waves (3.9%) died suddenly while watching television at approximately 10:00 PM during the follow-up period of 6.2 ± 2.7 years. The long-term recurrence rate was significantly higher in patients with J waves ($P = .0173$).

Discussion

Our VF population showed a circadian pattern of VF occurrence with the following 2 peaks: early morning and late evening. The QT (corrected QT) interval was shorter in

Table 2 Clinical and ECG characteristics of patients with IVF according to the presence of J waves

Characteristic	Patients with J waves (n = 30)	Patients without J waves (n = 34)	P
Age (y)	41.7 ± 15.9	42.7±19.0	.8120
Sex: male	27 (90.0)	31 (91.2)	.8721
FH of SCD	3 (15.0)	4 (11.8)	.7345
VF induction	20 (66.7)	23 (67.6)	.9336
ES	13 (43.3)	1 (2.9)	<.0001
ECG parameters			
RR interval (ms)	922 ± 190	931 ± 145	.8559
PR interval (ms)	169 ± 38	166 ± 25	.6672
QRS duration (ms)	102 ± 13	93 ± 13	.0234
QT interval (ms)	380 ± 29	390 ± 26	.1866
QTc interval ($ms^{1/2}$)	394 ± 38	407 ± 29	.1732
J wave (mV)	0.31 ± 0.15	—	—
VF occurrence (%)			
Midnight to 6:00 AM	46.7	17.6	.0124
10:00 PM to 6:00 AM	50.0	20.6	.0064

Values are presented as mean ± SD or as n (%).
Abbreviations are the same as in Table 1.

patients with nocturnal VF, and QRS duration was prolonged in those with J waves. The circadian pattern was affected by the presence of J waves, and VF occurred predominantly during the nocturnal period and recurred more frequently in patients with J waves.

BS patients are known to experience VF more frequently at night than during the remainder of the day.[21,22] Haïssaguerre et al[6] showed that 12 of 64 IVF patients with J waves (19%) experienced sudden cardiac arrest during sleep, whereas only 6 of 142 VF patients without J waves (4%) experienced sudden cardiac arrest during that time. Nam et al[23] reported 5 patients with VF storm and J waves, 3 of which experienced VF during the night hours and 1 during both night and day hours. In addition, Kim et al[24] observed that ventricular tachyarrhythmia (cardiac arrest plus appropriate shock) showed a significant nocturnal distribution ($P < .01$), and during the follow-up period of 6.4 ± 3.6 years, 5 of 14 patients with J waves (36%) experienced appropriate shocks with a significant nocturnal peak ($P < .0001$). These findings were confirmed in the present study.

Many case studies have shown that J waves are present in association with IVF. The dynamic changes of J waves were known to occur in IVF and were closely related to VF occurrence.[6,8–10] Augmentation of the J-wave amplitude is common before VF occurrence. In an approximately half of the patients with IVF, augmentation of J waves can be observed at slower heart rates or after sudden pauses: this phenomenon is known as bradycardia-dependent augmentation, which seems to be one of the characteristics of J waves in patients with IVF.[5,6,10] In addition to augmentation of J waves observed before VF occurrence, they may show transient nature. Actually, in 5 of 40 patients with IVF, J waves disappeared spontaneously within weeks.[9,10]

J waves have been shown to have circadian rhythmicity: they were augmented at night, and this was considered a result of enhanced vagal activity or slowing of the heart rate.[25–27] Although there is a controversy concerning the genesis of J waves,[4,28–30] the dominant occurrence of nocturnal VF in patients with J wave would suggest a significant linkage between VF and early repolarization abnormality.

Acute cardiovascular events, including sudden cardiac death, exhibit a circadian pattern featuring a peak in the morning.[19,20] In a meta-analysis of sudden cardiac death in the general population, it was found that VF and sudden cardiac arrest occur during the daytime in the majority (85.4%) of patients and occurred during the nocturnal period in only 14.6% among 13,591 patients.[31] Compared to the incidence of nocturnal sudden cardiac death in this meta-analysis,[31] VF was occurring more often during the nocturnal period in our patients with IVF than in the general population: 46.7% vs 14.6%. However, when J waves were absent, VF episodes of IVF patients occurred at a rate similar to that of the general population during the nocturnal period: 17.6% vs 14.6%.

In summary, IVF patients with J waves were more likely to suffer from nocturnal occurrence of VF. Furthermore, the presence of J waves on admission may be a hallmark of VF recurrence and it may be a risk factor for long-term arrhythmia recurrence in patients with IVF.

Study limitations

This study involves only a small number of cases and needs further confirmation in a larger number of patients. However, the present study included the largest number of patients with IVF studied in an analysis of the circadian pattern of VF occurrence so far, and the results are consistent with those case studies reported previously.[6,23,24] Patients with IVF who had early repolarization syndrome was reported to show a seasonal peak in appropriate shocks from spring to summer,[24] but the present study focused on the diurnal variation. Genetic screening is important for (1) the elucidation of the mechanism of VF in IVF and (2) the establishment of proper arrhythmia management. Although early repolarization patterns are heritable in the general population,[32] gene mutations have been reported only in sporadic cases of patients with IVF[33–35] and the yield of genetic screening is extremely limited at present.[36]

Conclusion

In patients with IVF, the nocturnal incidence of VF was higher in patients with J waves than in patients without J waves, which were associated with VF storms and VF recurrence during the follow-up period.

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CLINICAL PERSPECTIVES

The circadian pattern of ventricular fibrillation (VF) episodes is relatively well known in Brugada syndrome, and an increase in the nocturnal vagal activity/sympathetic activity is considered an underlying arrhythmogenesis of Brugada syndrome. However, the circadian pattern of VF occurrences in non–Brugada-type idiopathic ventricular fibrillation (IVF) patients is poorly understood. This article examined the clinical and electrocardiographic characteristics of 64 IVF patients, and the circadian pattern of VF occurrences in relation to J waves. Although all IVF patients had 2 peaks at 6:00 AM and 8:00 PM for the cardiac events or sudden cardiac arrest observed in the general population, the presence of J waves was associated with increased nocturnal VF episodes with a peak in the early morning. J waves were also associated with the recurrence of VF soon after hospitalization. Isoproterenol was effective in controlling VF and attenuated the J-wave amplitude. In addition, the presence of J waves was a risk for VF recurrence during follow-up, and thus implantable cardioverter-defibrillator implantations were mandatory. The nocturnal VF occurrence was less, and the long-term recurrence rate was lower in IVF patients without J waves. When physicians care for IVF patients with J waves, proper management is essential for VF occurring during the nocturnal period, for impending recurrences of VF storms, and for a high risk of chronic VF recurrences. The efficacy of drugs proven to be effective in Brugada syndrome and non–pharmacological-like catheter ablation for VF-triggered ventricular arrhythmias need to be assessed.

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Circumstances and Outcomes of Out-Of-Hospital Cardiac Arrest in Elementary and Middle School Students in the Era of Public-Access Defibrillation

– Implications for Emergency Preparedness in Schools –

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Background: Circumstances and outcomes of out-of-hospital cardiac arrest (OHCA) in elementary and middle school students while at school in the era of public-access defibrillation are unknown.

Methods and Results: We conducted a nationwide hospital-based survey of elementary and middle school students who had had OHCA of cardiac origin and received prehospital resuscitation in 2005–2009. Among 58 cases recruited, 90% were witnessed by bystanders; 86% had ventricular fibrillation as the initial rhythm; 74% were resuscitated by bystanders; 24% were defibrillated by bystanders; 55% occurred at school; 66% were exercise-related; 48% were followed up before the event; 67% had structural heart disease. In total, 53% of overall patients and 79% of those initially defibrillated by bystanders had a favorable neurological outcome. Patients were more likely to be defibrillated by bystanders (38% vs. 8%, P=0.012) and had a more favorable neurological outcome in schools (69% vs. 35%, P=0.017) than in other locations. The majority of arrests in schools were exercise-related (84% vs. 42%, P=0.001), occurred at sports venues, and students were resuscitated by teachers; half of the cases at school occurred in patients with a pre-event follow-up.

Conclusions: After OHCA, children were more likely to be defibrillated by bystanders and had a better outcome in schools than in other locations, which may be relevant to the circumstances of events.

Key Words: Defibrillation; Pediatric arrhythmias; Resuscitation; Sudden cardiac death

Sudden cardiac death in elementary and middle school students is a rare but devastating condition that has a tremendous effect on the family and local community, including schools, parent groups and family doctors.[1–7] Previously, early recognition and management of the underlying disease was believed to be the only possible approach toward preventing such events.[8,9] Recently, emergency response at school using automated external defibrillators (AED) has been con-

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sidered a potentially effective strategy,[10] because multiple studies, including a randomized trial, have demonstrated that public-access defibrillation (PAD) improves the outcome among adults after out-of-hospital cardiac arrest (OHCA) in specific public locations.[11–14] Schools have been regarded as particularly advantageous locations for an emergency responses with respect to the high proportion of witnessed arrests, bystander cardiopulmonary resuscitation (CPR), and bystander use of AED.[2,15] Although few studies have addressed the effect of PAD on cardiac arrests in students at school, a recent questionnaire survey demonstrated a substantial proportion of high-school athletes with sudden arrest survived to hospital discharge when early defibrillation with CPR was provided at sports venues staffed by athletic trainers.[15] However, the effect of PAD on OHCA in 'ordinary elementary and middle school students' at school and the related circumstances and outcome in the school setting are largely unknown.[1,16] This question is important because it could be the rationale for efficient placement of AED and focused training of staff at schools.[1–6,16]

Editorial p????

Since the use of AEDs by any citizen was approved in July 2004, the number of public-access AED devices in Japan has increased to 203,924 in 2009;[17] as many as 28.9% of those public-access AEDs in Japan were deployed in schools: nationwide, AEDs were placed in up to 72.0% and 89.8% of elementary and middle schools, respectively, by 2009.[18,19] Despite perceived concern over the low prevalence of ventricular fibrillation (VF) in children and the low success rate in defibrillating young athletes even in VF,[7,20,21] recent Japanese Utstein studies demonstrated that early defibrillation was associated with improved outcome in these children after cardiac OHCA.[6,22] However, the lack of a more detailed reporting system of OHCA, including specific location (ie, in schools), cardiac etiology, and related circumstances (high-risk situation, location, and population), has hindered the investigation of such issues in elementary and middle school students.[1–6,16]

We therefore investigated whether elementary and middle school students after OHCA of cardiac origin are more likely to be defibrillated by bystanders and exhibit more favorable neurological outcome in schools than in other locations, and under what circumstances this occurs. We conducted a nationwide hospital-based observational study of such students who had OHCA of cardiac origin in Japan.

Methods

Study Design

This was a retrospective, nationwide hospital-based questionnaire survey of OHCA of definitive or presumed cardiac origin in elementary and middle school students who were treated by emergency medical service (EMS) personnel and transported to hospitals between January 2005 and December 2009. This was an official research project endorsed by the Japanese Society for Pediatric Electrocardiography, a branch of the Japanese Society for Pediatric Cardiology and Cardiac Surgery. The ethics committee in the Mie University Graduate School of Medicine approved this study.

Study Setting

The EMS system and training programs for CPR/AED use in Japan have been reported previously in detail.[23,24] Briefly, Japan has an area of approximately 378,000 km^2, with a population of 127 million in 2005. There were 807 fire stations with a dispatch center in 2007. EMS is provided by municipal governments. Life support is provided around the clock by the local EMS system. The placement of AEDs in public areas was driven by either public or private initiatives.[25] Elementary (grades 1–6 at 6–12 years of age) and middle (grades 7–9 at 12–15 years of age) school education is compulsory in Japan. The cumulative number of public-access AEDs, excluding those in medical facilities and EMS institutions, increased from 9,906 to 203,924 (160.6/100,000 population) during the 5-year study period.[17] A total of 96.5% of public-access AEDs are located in public locations, 28.9% in schools.[18] The proportion of elementary and middle schools equipped with at least 1 AED device among all private and public schools across Japan increased from 18.1% and 38.3% in 2007 to 72.0% and 89.8%, respectively, in 2009.[19] Teachers and other school staff participated in CPR training programs conducted by EMS providers or other instructors, voluntarily or under the guidance of local school boards. In Japan, approximately 1.4–1.5 million citizens per year participate in CPR/AED training programs, which are typically provided by local fire departments.[26] Mandatory school ECG screening was legislated by the national government in 1995 and has been performed for all first graders in elementary and middle schools across Japan.[27]

Data Collection

Questionnaires were sent to 191 hospitals across Japan, including all hospitals registered as teaching hospitals by the Japanese Society for Pediatric Cardiology and Cardiac Surgery or to which any councilor of the society belonged, and an additional 34 hospitals, from which any doctor in any scientific meeting reported web-searchable OHCA cases that met the criteria for inclusion. Registry data were collected retrospectively by a doctor in charge with the aid of hospital records and pertinent EMS information.

Definition of Terms in the Questionnaire

The terms and questionnaire items were defined in accordance with the Utstein-style guideline in the all-Japan registry, which included initial cardiac rhythm, return of spontaneous circulation (ROSC) before hospital arrival, 1-month survival, and neurological status after the event [6,23,24] The specific items in the questionnaire are reported in detail in Supplementary File: Methods.

Cardiac arrest was defined as cessation of cardiac mechanical activity confirmed by the absence of signs of circulation.[23,28,29] The arrest was presumed to be of cardiac origin unless of noncardiac origin (respiratory disease, malignant tumors, central nervous system disorders, anaphylaxis, endocrine disease, etc.), or external (traffic accident, trauma, hanging, drug overdose, bleeding, asphyxia, etc.), which was determined clinically by the physician in charge according to the EMS information.[23,28,29] Commotio cordis was therefore excluded in this study. When a layperson delivered defibrillation by an AED, the initial rhythm of the patient was regarded as VF, including pulseless ventricular tachycardia.[6,23,24] A patient initially defibrillated by a bystander was defined as one in which a public-access AED was used and defibrillation was delivered; if the public-access AED was applied but defibrillation was not delivered, the patient was not included in this category.[6,23,24] Exercise was defined as any activity that would increase heart rate: jogging, swimming, playing sport, cycling or stair climbing were regarded as exercise-related, whereas walking, standing or sitting was not regarded as exertional.[2] Neurological outcome at 1 month after successful resuscitation was determined by the doctor in charge, using the Cerebral Performance Category (CPC)

Table 1. Clinical characteristics and outcomes of out-of-hospital cardiac arrests in school children at or out of school

	Total	At school	Out of school	P value
No. of events, n	58	32 (55)	26 (45)	
Male gender, n (%)	37 (64)	20 (63)	17 (65)	1.00
Median age (interquartiles)	12 (11, 14)	13 (11, 14)	12 (9, 14)	0.24
Calendar year 07-09, n (%)	43 (74)	24 (75)	19 (73.1)	1.00
Bystander witness, n (%)	52 (90)	31 (97)	21 (81)	0.08
Nonfamily witness, n (%)	43 (74)	31 (97)	12 (46)	<0.001
Events in public locations, n (%)	48 (83)	32 (100)	16 (62)	<0.001
Initial VF, n (%)	48 (86)	28 (94)	20 (77)	0.13
Bystander's CPR, n (%)	43 (74)	27 (84)	16 (62)	0.07
AED use, n (%)	44 (76)	26 (81)	18 (69)	0.36
Bystander AED, n (%)	14 (24)	12 (38)	2 (8)	0.01
EMS AED, n (%)	30 (52)	14 (44)	16 (62)	0.20
Exercise-related, n (%)	38 (66)	27 (84)	11 (42)	0.001
Followed-up cases, n (%)	28 (48)	16 (50)	12 (46)	0.77
Favorable neurological outcome, n (%)	31 (53)	22 (69)	9 (35)	0.02
Survival at one month	42 (72)	23 (72)	19 (73)	1.00
Pre-hospital ROSC	33 (59)	20 (65)	13 (52)	0.42

Number among available data with the percentage in parenthesis was shown.
AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation; VF, ventricular fibrillation.
Missing data on cases of initial VF at school (n=2) and pre-hospital ROSC at and out of school (1 each) were included, with percentages calculated based on the available data.

Table 2. Clinical and Outcome Parameters in Subgroups of Patients in the Japanese Pediatric Utstein Study

Parameter	Public location n=129	Private location n=101	P value
By presumed location of arrest			
Defibrillated by			
Bystander, n (%)	27 (21)	2 (2)	<0.001
EMS, n (%)	71 (55)	38 (38)	0.009
Favorable neurological outcome, n (%)	48 (37)	15 (15)	<0.001
Survival at 1 month, n (%)	62 (48)	22 (22)	<0.001
Prehospital ROSC, n (%)	46 (36)	20 (20)	0.008
Parameter	**Bystander n=29**	**EMS n=109**	**P value**
By bystander or EMS personnel who defibrillated the victim			
Collapse to CPR time, min	2.9±3.7	5.0±5.6	0.061
Collapse to AED time, min	3.3±3.7	12.9±5.8	<0.001
Favorable neurological outcome, n (%)	17 (59)	39 (36)	0.026
Survival at 1 month, n (%)	20 (69)	52 (48)	0.042
Prehospital ROSC, n (%)	19 (66)	39 (36)	0.004

Data are n (%). Family member-witnessed arrests were presumed to be in a private location; non-family member-witnessed arrests were presumed to be in a public location.
Abbreviations as in Table 1.

scale in which category 1 represents good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; category 5, death.[23,28,29] CPC1–2 was regarded as a favorable neurological outcome.

Statistical Analysis

All statistical analyses were performed with the SPSS statistical package, version 16.0J (PASW Statistics 18.0). Continuous data are reported as median and interquartile ranges. The significance of any differences among 2 or more than 2 groups was assessed by the Mann-Whitney U test or by the Kruskal-Wallis test, followed by Mann-Whitney U test, adjusted for multiple comparisons. Categorical data are expressed as a value or frequency of occurrence. The difference of the proportions of categorical variables among groups was assessed by chi-square analysis. All tests were 2-tailed, and $P<0.05$ was considered to indicate statistical significance.

Results

The primary response rate in the present questionnaire survey was 57%; 58 elementary and middle school students (median age [interquartile range]: 12 years [11–14]; males: 64%) after an

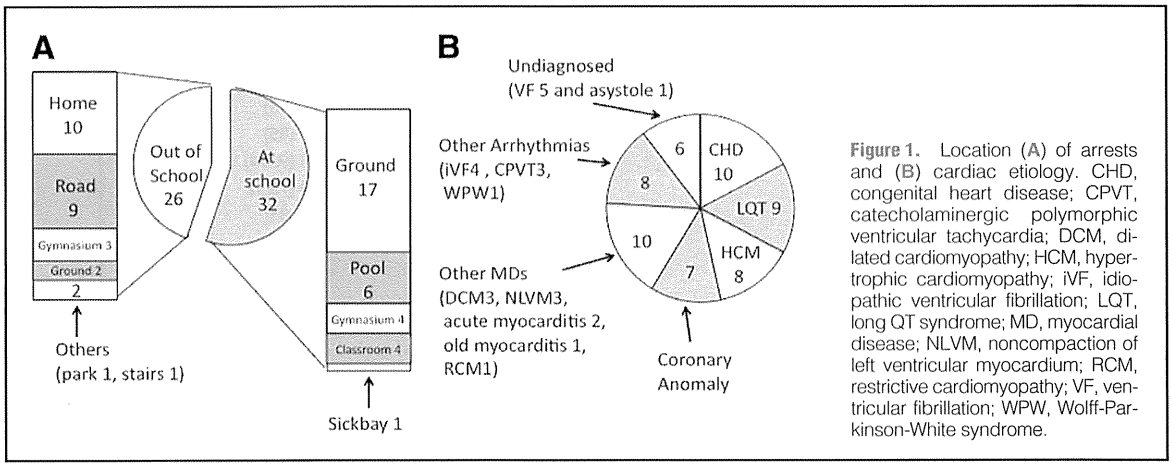

Figure 1. Location (A) of arrests and (B) cardiac etiology. CHD, congenital heart disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; iVF, idiopathic ventricular fibrillation; LQT, long QT syndrome; MD, myocardial disease; NLVM, noncompaction of left ventricular myocardium; RCM, restrictive cardiomyopathy; VF, ventricular fibrillation; WPW, Wolff-Parkinson-White syndrome.

OHCA with a definitive cardiac diagnosis (n=52) or of presumed cardiac origin (n=6) were recruited (Table 1): 52 (90%) were witnessed by bystanders (9 by family members and 43 by non-family members [30 by school teachers and 13 by others]); 48/56 patients (86%) had VF as the first documented rhythm (pulseless electrical activity in 2, asystole in 6, unknown in 2); 43 (74%) received bystander CPR (8 from family members and 35 from non-family members [27 from school teachers and 8 from others]); 44 (76%) received AED-based prehospital defibrillation (30 from EMS personnel and 14 from bystanders [11 from school teachers and 3 from other non-family members]). A total of 31 patients (53%) had a favorable neurological outcome, 42 (72%) survived 1 month after OHCA, and 33/56 (59%) had ROSC before arrival at the hospital. Among the patients initially defibrillated by a bystander, 11/14 (79%) exhibited a favorable neurological outcome. The proportion of prehospital ROSC was higher in patients with a favorable neurological outcome (26/29, 90%, P<0.001) than in those without a favorable neurological outcome (7/27, 26%). The proportion of prehospital ROSC tended to be higher in patients defibrillated by bystanders (11/13, 85%, P=0.11) than in those defibrillated by EMS personnel (18/30, 60%). The distribution of patients by school grade is illustrated in Figure S1. As a reference for this study, clinical and outcome parameters in subgroups of patients in an all-Japan population-level study of the same age population during the same study period are reported in Table 2.[6]

Characteristics of OHCA at School

Of the 58 patients, 32 (55%) had their OHCA at school (Table 1), which accounted for 67% of total public location arrests and comprised 31 non-family member-witnessed arrests and 1 unwitnessed arrest. Of the 43 non-family member-witnessed arrests, 31 occurred at school, 11 in other public locations, and 1 at home. Compared with an arrest out of school, an arrest at school was more likely to be witnessed by a non-family member (P<0.001), occur in a public location (P<0.001), be initially defibrillated by a bystander (P=0.01) but not by EMS, be witnessed by a bystander (P=0.08), and receive CPR from a bystander (P=0.07). In schools, teachers witnessed all 31 witnessed cases, treated all 27 cases resuscitated by a bystander, and defibrillated all 12 cases initially shocked by a bystander, except 1 case. An arrest at school was more likely to be exercise-related (84% vs. 42%, P=0.001), and to be in initial VF (94% vs. 77%, P=0.13) than out of school, but not associated with sex, age, calendar year, or pre-event follow-up status (50% vs. 46%, P=0.77). In schools, arrests at sports venues, including the ground, pool, and gymnasium, accounted for 84% of arrests, while arrests at sports venues out of school accounted for 19% (Figure 1). A total of 73% arrests out of school occurred at home or on the road, where AED devices are rarely located: among 9 arrests on the road, 6 students were traveling to or from school. Among all 14 events in patients initially defibrillated by a bystander, 11 occurred at sports venues and 1 at another location in school, while 2 were in public locations out of school. An arrest at school was associated with a higher proportion of favorable neurological outcome 1 month after OHCA than out of school (P=0.02) (Table 1).

Cardiac Etiology and Circumstances of OHCA in School Children

Figure 1 depicts the diagnosis of the cardiac disorders. Among all 58 arrests, 52 (90%), comprising 41 of 42 survivors and 11 of 16 non-survivors, were diagnosed. Of these 52 diagnosed cases, structural and nonstructural heart disease accounted for 67% and 33%, respectively. Cardiac etiology according to exercise status and follow-up status is shown in Figure 2. Arrests that occurred during or just after exercise accounted for 66%, events that occurred at rest or during walking accounted for 26%, and events that occurred during sleeping accounted for 7%. All arrests in the coronary anomaly and catecholaminergic polymorphic ventricular tachycardia (CPVT) categories were exercise-related, whereas 50% of cases of congenital heart disease (CHD) and of hypertrophic cardiomyopathy (HCM) were exercise-related. Cases of follow-up for chronic heart disease before the event accounted for 48%. All 10 CHD cases, 6 of the 8 HCM cases, 5 of the 8 other myocardial diseases, excluding 2 acute myocarditis cases, and 4 of the 9 cases of long QT syndrome were followed up. No cases of coronary anomaly, CPVT, or idiopathic VF were followed up. The proportion of these 3 diseases, which can exhibit apparently normal resting ECG, accounted for 47% of the total cases with no pre-event follow-up (Figure 2). There was a tendency toward a lower proportion of exercise-related events in followed cases (54% vs. 77%, P=0.06) than in unfollowed cases (Table 3). OHCAs among the unfollowed cases of arrests at school, which were almost always exercise-related (94%), were frequently associated with these 3 diseases which could exhibit apparently normal resting ECG (63%) (Table 3). Among 27 exercise-related cases of arrests at

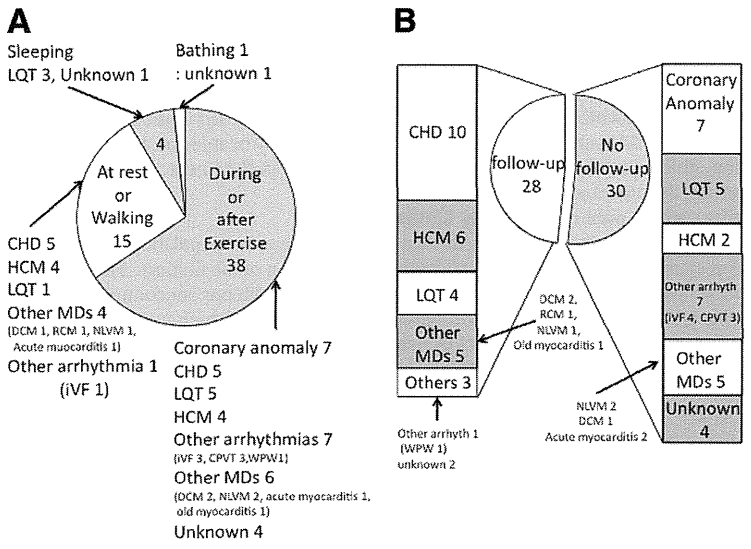

Figure 2. Cardiac etiology by (A) exercise status and (B) follow-up status. CHD, congenital heart disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; iVF, idiopathic ventricular fibrillation; LQT, long QT syndrome; MD, myocardial disease; NLVM, noncompaction of left ventricular myocardium; RCM, restrictive cardiomyopathy; VF, ventricular fibrillation; WPW, Wolff-Parkinson-White syndrome.

Table 3. Cardiac Disease and Exercise Status by Location and Follow-up of Arrest

	At school (n=32)	Out of school (n=26)
Follow-up (28)	(n=16)	(n=12)
	Exercise-related (n=12)	Exercise-related (n=3)
	HCM (4), CHD (3), LQT (3), Other MD (3: DCM 1, NLVM 1, old myocarditis 1), Other arrhythmia (1: WPW), Unknown (2)	CHD (7), HCM (2), LQT (1), Other MD (2: DCM 1, RCM 1)
No follow-up (n=30)	(n=16)	(n=14)
	Exercise-related (n=15)	Exercise-related (n=8)
	Coronary anomaly (5), HCM (2), LQT (2), Other arrhythmia (5: iVF 3, CPVT 2), Other MD (1: DCM), Unknown (1)	LQT (3), Coronary anomaly (2), Other MD (4: NLVM 2, acute carditis 2), Other arrhythmia (2: iVF 1, CPVT 1), Unknown (3)

CHD, congenital heart disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; iVF, idiopathic ventricular fibrillation; LQT, long QT syndrome; MD, myocardial disease; NLVM, noncompaction of left ventricular myocardium; RCM, restrictive cardiomyopathy; WPW, Wolff-Parkinson-White syndrome.

school, the likelihood of defibrillation by bystanders was similar between the followed cases and ostensibly healthy students (42% vs. 40%, P=0.93) (data not shown). The clinical and outcome parameters according to disease category and cardiac etiology according to the time of day and location of arrest are described in detail in Table S1, Figure S2 and the text.

Discussion

According to previous Japanese Utstein registry studies, which included all age groups, it is adolescents and younger school-age children who are most likely to be defibrillated by a bystander and have a favorable neurological outcome.[6,22] However, the specific locations of arrests and circumstances of events related to PAD are unknown. In the present survey, we demonstrated that elementary and middle school students were more likely to benefit from defibrillation by bystanders after OHCA and exhibited a more favorable neurological outcome for arrests occurring in schools than in other locations, suggesting that school campuses might be a specific location that is highly efficient for CPR with defibrillation by bystanders. The majority of arrests in schools were exercise-related, occurred at sports venues, and were witnessed and resuscitated by teachers, which could support prioritization of the placement of AED in these locations and the focused training of school teachers, especially those in charge of physical exercise, in CPR with AED. Patients with associated chronic cardiac disease in the pre-event follow-up accounted for half of the arrests at school, suggesting that such a subgroup may be at high risk for OHCA at school.

OHCA at School in the Era of PAD

In the present study, we demonstrated that an arrest in children at school was associated with a high proportion of AED use by bystanders and a favorable neurological outcome; this is in contrast with the low rate of defibrillation by bystanders out of school. These findings are consistent with our concomitant pediatric Utstein study, in which there was a high rate of AED use by bystanders (21%) and a favorable neurological outcome (37%) after OHCA occurred in a public location, although the specific location of arrests was not determined in that study.[6] These findings are also consistent with a recent sharp decline of the incidence of sudden cardiac death in children under school supervision in the Japan Sport Council database, although the incidence of OHCA or the number of bystander's using AEDs is unknown.[30] The advantage of school campuses for emergency preparedness is consistent with a population-based Seattle/King

County study in which arrests on school campus were characterized by a higher rate of witnessed arrest (79%), bystander CPR (74%), and survival to hospital discharge (39%), although that study mainly focused on the adult population with few cases initially defibrillated by a bystander.[2] It is also consistent with a questionnaire study of US high-school athletes, in which 93% (13/14) received AED defibrillation and 64% (9/14) survived to hospital discharge, although the non-athlete population was not addressed in that study.[15] Therefore, the outcome in schools could be comparable to that in other specific public locations, including casinos, airlines, and airports, where the favorable effect of PAD has been highly appreciated.[11–14] The high rate of initial VF in the present study was consistent with that in 2 other school-based studies [Seattle/King study (78%) and the US high-school study (83%)], as well as in our pediatric Utstein study (71% in public location arrests).[2,6,15] In addition, the proportion of VF did not vary significantly with the underlying disease category in the present study, suggesting the therapeutic potential of early defibrillation overall in children after arrests at school.

The non-athletic level of exercise in schools,[2,5] as well as strenuous exercise such as by competitive athletes in high school or university, or by young adults,[15,21,31,32] has been considered a trigger for OHCA. As the proportion of exercise-related arrests was higher in than out of school in the present study, even regular exercise by elementary and middle school students at school poses a risk for an arrest in such children; sports venues were a high-risk location of arrests in schools; however, bystander CPR and defibrillation performed by teachers in such a situation worked reasonably well. These findings support prioritization of AED placement accessible to these locations in schools and focused training of school teachers, especially those in charge of physical exercise, in CPR with AED.

Cardiac Etiology and Circumstances of OHCA in School Children

Cardiac disorders related to sudden cardiac death in school children have been extrapolated from pathology-based studies of young athletes and non-athletes up to the age of 35 in Italy, the USA, and the UK.[5,32–34] In those studies, structural heart disease, including HCM (4–36%), coronary anomaly (≤17%), myocarditis (3–12%), and arrhythmogenic right ventricular cardiomyopathy (≤14%), was the predominant cause of arrests; 6–29.2% of arrests were unexplained, and presumed to be caused by arrhythmia.[5,32–34] The relatively high proportion of CHD in the present study was consistent with the findings in the recent King County study, which included non-athletic children with chronic diseases (21–23%).[5] The inclusion of specific arrhythmic disorders in the present study was newly derived from clinically diagnosed aborted sudden death cases recruited nationwide. Thus, this study presents the cardiac etiology of OHCAs in a specific school-age population, which could be relevant to the understanding of arrests in such students.

Because we have demonstrated that approximately half of all arrests, and of those at school, occurred in students with a pre-event follow-up of cardiac disease, as in a previous school-based study,[2] the recognition of such a high-risk group may have implication in emergency responses at school. Despite a lower proportion of exercise-related events in followed cases, which may be explained by the effect of withdrawal from exercise in such cases or the exercise-related characteristics of the disease,[32–36] 'pre-event awareness of diseases', including HCM and long QT syndrome, could aid in alerting school staff to otherwise unpredictable events in schools. Conversely, as OHCA in ostensibly healthy children at school was mostly exercise-related, the secondary prevention of cardiac death by using AED at sports venues may play an essential role. Although the likelihood of defibrillation by bystanders was in fact similar between the followed cases and ostensibly healthy children among the exercise-related cases of arrests at school in the present study, the recognition of a high-risk patient, as well as a high-risk situation and venue, may be relevant to optimizing the outcome of OHCA at school in the future.

Study Limitations

First, this was a retrospective, nonpopulation-based study, which may affect the interpretation of the findings. However, the present findings are consistent with our concomitant pediatric population-based Utstein study, in which we demonstrated a high rate of bystander AED use and favorable neurological outcomes after OHCA occurring in public locations.[6,22] Second, specific information on the scope of the budgetary barriers and logistic issues (ie, the locations of AEDs, training schedule for teachers) involved in implementing and refining AED/CPR programs at the national level in Japan is unavailable. Third, cardiac etiology of OHCA in followed and unfollowed patients in the present study could be influenced by the school ECG screening in Japan, although the role of the school ECG screening system was not specifically addressed.[27] Fourth, the present study focused on the issue in children, not adults, in schools.[2,16] Fifth, there might be unmeasured confounding factors (ie, quality of bystander's CPR) that might influence outcomes.[6,23,37]

Conclusions

OHCA in school children is a rare event, but one of great public concern. The present study is the first to characterize cardiac arrest in ordinary elementary and middle school children in or out of school in the era of PAD, which could be relevant to the recognition of high-risk groups, the efficient placement of AEDs and the focused training of staff (CPR with AED use) in schools. The present findings warrant population-based studies on the role of CPR with AED use and related circumstances of events in schools.[8,10,22]

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Disclosures

We declare that we have no conflicts of interest.

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Supplementary Files

Supplementary File 1

Methods.

Figure S1. Distribution of patients by school grade.

Figure S2. (A) Cardiac etiology by the time of day of arrest.

Table S1. Clinical and outcome parameters by disease category (n=52)

Please find supplementary file(s);
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