2.2. Tonic block of WT and N406S channels

We first looked for the differences in lidocaine interaction with inactivated WT and N406S channels, because the N406S mutation shifts the voltage-dependence of steady-state availability of the expressed channel [9]. Fig. 2 shows that lidocaine induced marked hyperpolarizing shifts in the steady-state availability for both WT and N406S channels. The effect of lidocaine on inactivation for N406S channel was slightly smaller than that for WT. On the other hand, lidocaine did not affect the voltage-dependence of activation curve for WT or mutant channel (data not shown).

The lidocaine-induced shift in availability predicted a greater tonic block of WT vs. N406S channels at physiologically relevant holding potentials (Fig. 3). However, at clinically relevant concentrations of lidocaine (1–5 μg/ml ≅ 4–20 μM), lidocaine could not discriminate between WT and N406S channels on the basis of tonic block.

2.3. Use-dependent block of WT and N406S channels

We next compared the blocked fractions that accumulated with repetitive activity when N406S mutant and WT channels were exposed to lidocaine (Fig. 4A). There was a statistically significant difference in use-dependent lidocaine block between N406S and WT channels over a broad frequency range (Fig. 4B).

2.4. Effects of N406S mutation on recovery from lidocaine block

The blocked fraction that accumulated as a consequence of repetitive channel activity is determined by a balance the time course of the onset of block (during depolarization) and the recovery from block (during repolarization) [13]. To understand the reduced sensitivity of the N406S channel to use-dependent block, we studied the effect of lidocaine on the time courses of recovery from the inactivated states. Lidocaine (100 μM) slowed the time course of recovery from

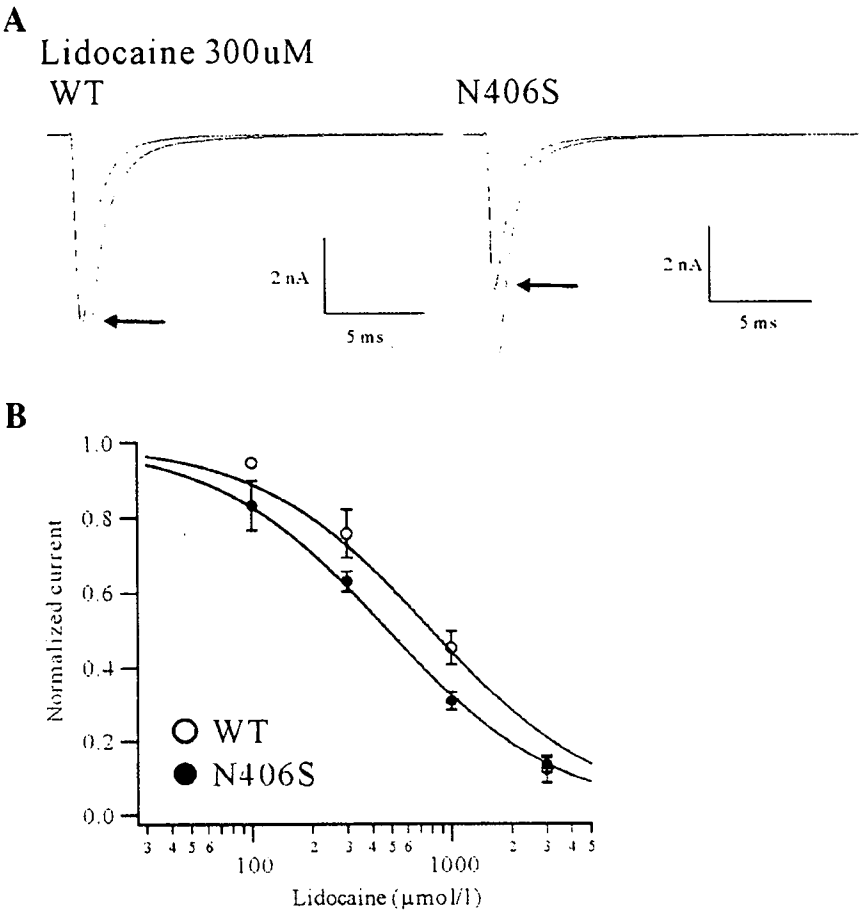


Fig. 3. Tonic block and use-dependent block of WT and N406S mutant channels. (A) Inhibition of sodium current elicited in HEK cells expressing WT or N406S channels with lidocaine. Traces show currents in control solution and after steady-state tonic block was attained (arrows). 2 to 4 min after cell superfusate was changed to one containing lidocaine (300 μM). (B) Concentration-dependence of tonic block of WT and N406S channels by lidocaine. Graph shows peak current after drug application, normalized to peak current in absence of drug, plotted as a function of drug concentration. Smooth lines are according to $1/(1+[\text{lidocaine}]/EC_{50})^{(n=2)}$. EC50 for lidocaine is 796 μM (WT) and 481 μM (N406S); $n=4$ cells per condition.

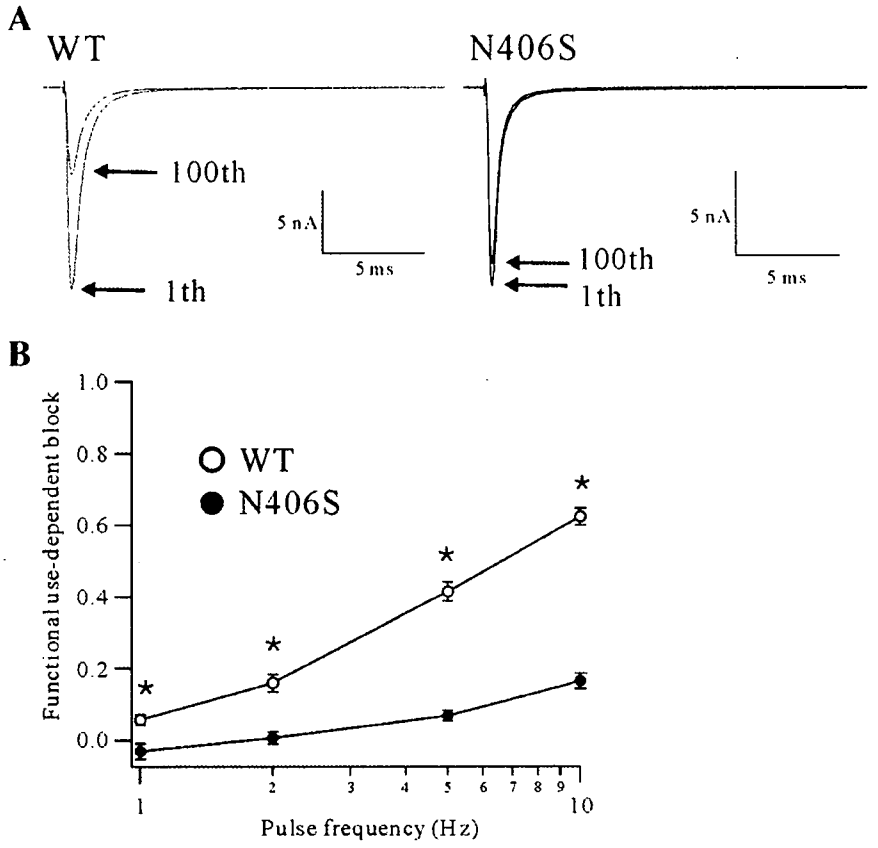


Fig. 4. (A) Frequency dependence of lidocaine block at fixed drug concentrations (100 μM). N406S mutation decreases sensitivity of channels to use-dependent block by lidocaine. (B) Graphs show peak currents of WT (open circles) and N406S (filled squares) during steady-state use-dependent block normalized to peak current during first pulse of train plotted against stimulus frequency. $n = 13$ cells per condition. The normalized residual peak I_{Na} in the presence of lidocaine were 94±1, 84±2, 58±2, and 37±2% for WT, and 100±2, 99±2, 93±1, and 83±2% for N406S at 1, 2, 5, and 10 Hz, respectively. *$P<0.01$.

the fast inactivation (induced by 20-ms depolarization pulses) similarly for N406S and WT (Fig. 5). On the other hand, lidocaine accelerated the time course of recovery from the intermediate inactivation (induced by 1000-ms depolarization pulses) for N406S (Table 1), whereas it delayed the time course for WT (Fig. 6). We studied the development of the intermediate inactivation by varying the duration of depolarizing pulse. A 20-ms repolarization to −120 mV was interposed between depolarizing pulse and test pulse to allow recovery from the fast inactivation. The time course was fitted by an exponential function very well and demonstrated faster development of the intermediate inactivation for N406S in the experiment without lidocaine [9], while the residual current for the N406S with lidocaine was larger than WT only after the long depolarizing pulse above 2000 ms (data not shown).

2.5. Activity-dependent loss of sodium channel availability by lidocaine

We tested for differences between WT and N406S channels in the response to lidocaine, when physiological long pulses were applied. WT channel inactivated more in the presence of lidocaine than in its absence. Unexpectedly, however, lidocaine reduced the activity-dependent loss for N406S (Fig. 7).

2.6. Mechanism of lidocaine effects for N406S channel

To understand the electrophysiological and pharmacological consequences of the N406S mutation, we constructed Markov models of the WT and N406S mutant sodium channels based on the experiment data of voltage-clamp recordings of sodium channels heterologously expressed in HEK 293 cells [9]. To evaluate the electropharmacological consequences of the N406S mutation, based on the experimental results of voltage-clamp recordings [9], we looked for parameters responsible for the gating defects (Fig. 8). First, we simulated the positive shift of the activation curves and steady-state activation by altering the voltage dependence of the activation transition rate α13. Changes of α11 or α12 also showed the same result as α13. Second, the leftward shift of the N406S recovery curve relative to WT indicated a faster recovery from fast inactivation. This shift provided a positive shift of steady-state inactivation. Both changes were simulated by increasing α3. Third, the slower recovery of

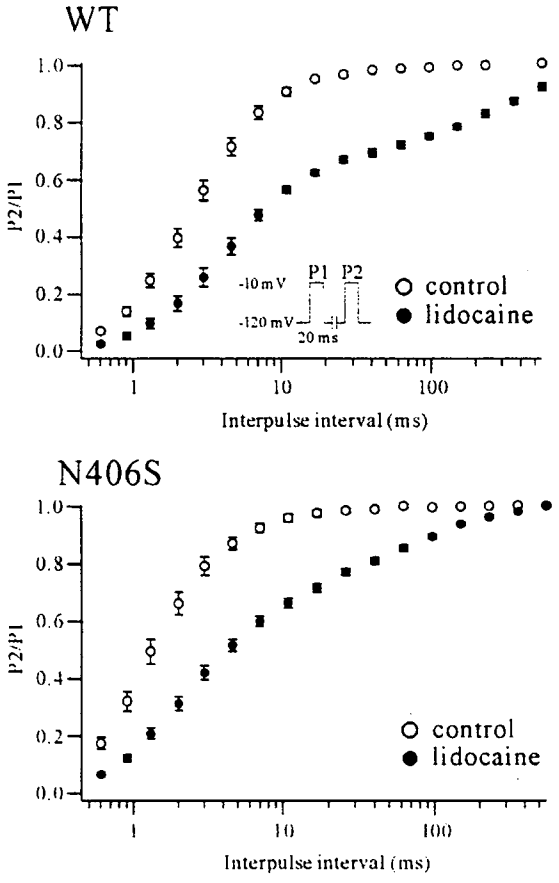


Fig. 5. Time course of recovery from the fast inactivation of WT ($n=14$) and N406S ($n=11$) was studied using the two-pulse protocol shown in the inset, in the absence (open circles) and in the presence (filled circles) of lidocaine (100 μM). The recovery from the fast inactivation for N406S is similar to WT and 1795insD (data not shown) in the presence of lidocaine.

N406S from intermediate inactivation could not be simulated by changing the transition rates between IF and IM1, because alterations of the transition rates between IF and IM1 resulted in a slower recovery from fast inactivation. But we could reproduce the slower recovery of N406S from intermediate inactivation, when the equilibrium point between IM1 and IM2 was shifted toward IM2, by changing the transition rates $\alpha 5$ and $\beta 5$. It was notable that each defect seems relatively independent, because altering a single gating parameter did not affect other simulation protocols.

When the changes in parameters ($\alpha 13$, $\alpha 3$, $\alpha 5$, $\beta 5$) were combined, we could successfully reproduce the N406S mutant channel characteristics. The experimentally measured values of $V_{1/2}$ for WT and N406S were −40.6 and −24.7 mV, respectively (a shift of 15.9 mV for N406S relative to WT). The simulated activation curve of N406S was shifted by 12 mV ($V_{1/2}=-20$ mV) relative to the WT curve ($V_{1/2}=-32$ mV). Both experiment and simulation show faster recovery from fast component of intermediate inactivation and slower recovery from the slow component of intermediate inactivation in N406S.

An important point is that we could reproduce the slower recovery of N406S from intermediate inactivation when the equilibrium point between IM1 and IM2 was shifted toward IM2. Lidocaine could prevent the N406S channel from going into IM2 state as this "deep" intermediate inactivation state. The recovery of lidocaine block for the mutant would be faster than that of "deep" intermediate inactivation.

3. Discussion

In this study, we demonstrated that lidocaine prevents the sodium channel with the N406 Brugada mutation from accumulating in the state of intermediate inactivation. The results imply that lidocaine might be effective for a group of patients with Brugada syndrome whose mutations are associated with the common receptor site for antiarrhythmic drugs.

The genetic basis of Brugada syndrome has been shown to be partly molecular defects in $Na_V1.5$ [4]. Many of the *SCN5A* mutations result in failure of the sodium channel to express [14,15]. Some of these mutations reduce sodium currents by shifting voltage dependence of activation or availability, or by enhancing intermediate inactivation [5].

We previously discovered an *SCN5A* missense mutation N406S, which was associated with gating defects of the depolarizing shift in the voltage-dependence of activation and the enhanced intermediate inactivation. Furthermore, N406S showed a unique property that it practically abolished the blocking actions of a class Ic sodium channel blocker. On the other hand, we did not have adequate clinical or experimental data how class Ib antiarrhythmic drugs could affect sodium channels with Brugada mutations. Class Ib antiarrhythmic drugs, lidocaine or mexiletine, are useful medical drugs for patients with long QT syndrome type 3 (LQT3) which is also caused by *SCN5A* mutations, because class Ib agents stabilize the inactivation states of the sodium channel and decrease persistent sodium currents which are characteristic of LQT3 [16]. We tested the effect of lidocaine on sodium channels with Brugada mutations. Unexpectedly, lidocaine prevented the N406 mutant channel from accumulating in the state of intermediate inactivation. Because the 1795insD mutant channel also has the accelerated intermediate inactivation, we analyzed how lidocaine could affect the intermediate inactivation of 1795insD. The effect of lidocaine on 1795insD was the same as for WT, and we could not detect the faster recovery as seen for N406S (data not shown). The simulation study for the N406S channel

Table 1
Recovery from intermediate inactivation and lidocaine block

	τ_f (ms)	τ_s (ms)	A_1 (%)	A_2 (%)
WT	4.7±0.4	152±39	87±1	13±1
WT−lidocaine	100±31	562±150	12±4	88±4
N406S	2.9±0.3	361±47	73±2	27±2
N406S−lidocaine	15±3	167±34 *	51±2	49±2

* N406S vs. N406S−lidocaine, $p<0.05$.

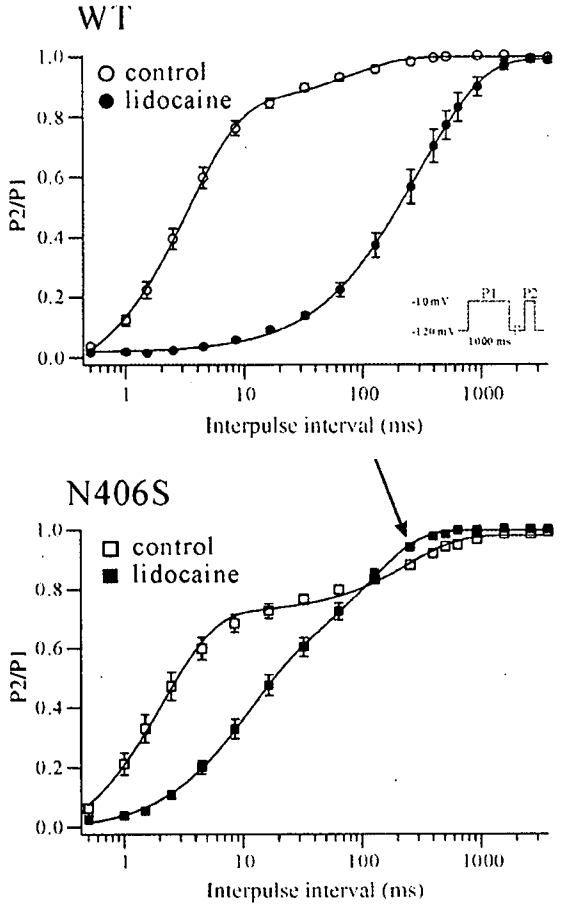


Fig. 6. Time course of recovery from the intermediate inactivation of WT (n=11) and N406S (n=9) was studied using the two-pulse protocol shown in the inset, in the absence (open circles/squares) and in the presence (filled circles/squares) of lidocaine. Fitting with a double-exponential function, $y=A_1\times(1-\exp[-t/\tau_1])+A_2\times(1-\exp[-t/\tau_2])$ yielded the time constants and fractional amplitudes (in percent) as follows: τ_1=4.7±0.4 ms (87±1%), τ_2=152±39 ms (13±1%) for WT; τ_1=100±31 ms (12±4%), τ_2=562±150 ms (88±4%) for WT with lidocaine; τ_1=2.9±0.3 ms (73±2%), τ_2=361±47 ms (27±2%) for N406S; τ_1=15±3 ms (51±2%), τ_2=167±34 ms (49±2%) for N406S with lidocaine, N406S vs. N406S+lidocaine, $p<0.05$. Arrow indicates that lidocaine accelerated the time course of recovery from the intermediate inactivation for N406S.

demonstrated that the mutant channel could accumulate in the "deep" intermediate inactivation state. We speculate that the recovery from lidocaine block for the N406S channel would be faster than that from the "deep" intermediate inactivation. The shape of the recovery from the fast inactivation is altered in N406S channel, but the change is not so much as that from the intermediate inactivation. A previous report [17] showed that lidocaine could increase the slope factor for the steady-state inactivation. Slope factors for both WT and N406S channels were significantly larger than those without lidocaine. The relative change in slope is significantly less in the N406S channel. We speculate that effects of lidocaine for N406S channel is reduced in the inactivation state judging from Fig. 6.

Despite substantial progress in the identification and characterization of Brugada syndrome over the past decade, relatively little progress has been made in the approach to therapy. Implantation of a cardioverter–defibrillator is the only established effective treatment for the syndrome [18,19]. This, however, is not an ideal solution for infants and young children or for adults residing in regions of the world where an implantable cardioverter–defibrillator is not an option because of economic constraints. The pharmacological approach to therapy is focused on a rebalancing of currents active in the early phases of the RV epicardial action potential so as to reduce the magnitude of the action potential notch and/or to restore the action potential dome. Experimental studies suggest that agents that block the transient outward current, such as quinidine or tedisamil, or agents that boost the calcium current (I_{Ca}), such as isoproterenol,

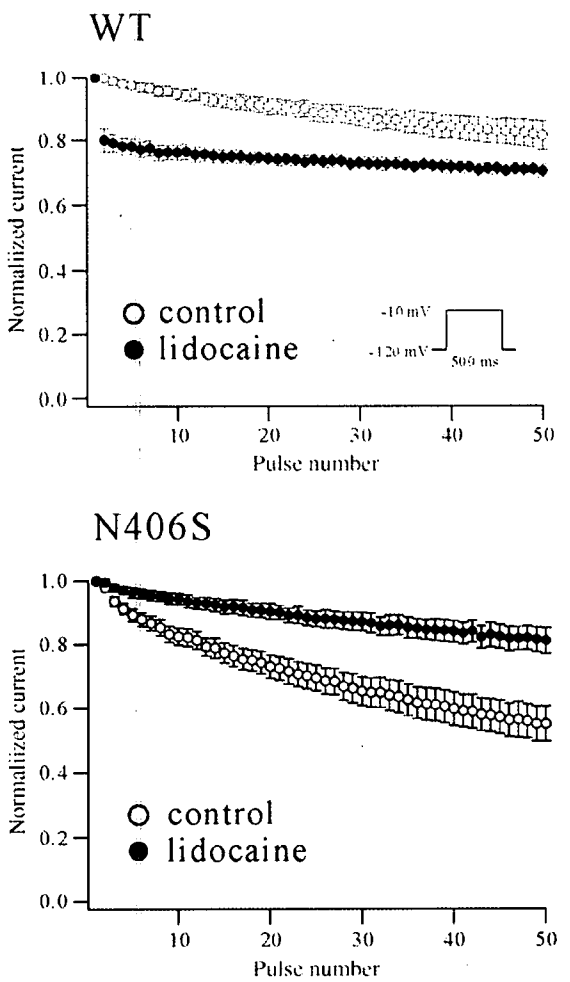
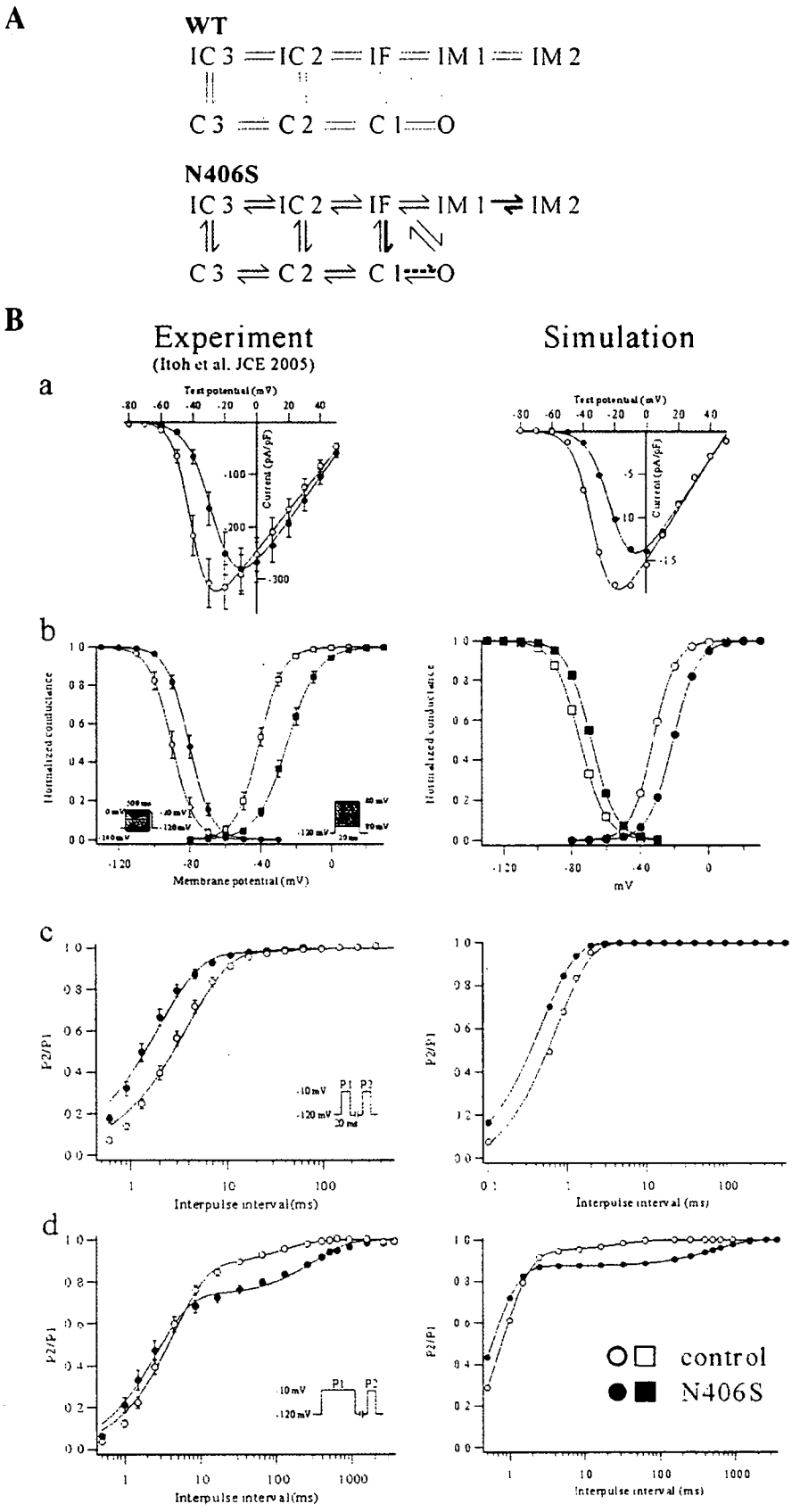


Fig. 7. Activity-dependent loss of channel availability of WT and N406S in the presence (filled circles) or absence (open circles) of lidocaine stimulated with 500-ms depolarization steps at 1 Hz. The normalized residual current levels recorded at the 50th pulse were 82±4% for control and 71±2% with lidocaine (filled, n=9) for WT ($p<0.05$), and 55±5% for control (open, n=9) and 81±4% with lidocaine (filled, n=9) for N406S ($p<0.001$). Surprisingly, activity-dependent loss of channel availability of N406S with lidocaine equal to that of WT at baseline.


A
WT
IC3 IC2 IF IM1 IM2
C3 C2 C1 O
N406S
IC3 IC2 IF IM1 IM2
C3 C2 C1 O
B
Experiment
(Itoh et al. JCE 2005)
Simulation
a
b
c
d
Test potential (mV)
Current (pA/pF)
Normalized conductance
Membrane potential (mV)
mV
P2/P1
Interpulse interval (ms)
control
N406S

may be useful [20,21]. Both have been shown to be effective in normalizing ST-segment elevation in patients with Brugada syndrome, particularly in children [22–24], but except for the study by Belhassen and colleagues [25,26] using quinidine, none have demonstrated long-term efficacy in the prevention of sudden death. A recent addition to the pharmacological armamentarium is the phosphodiesterase III inhibitor cilostazol [27], which normalizes the ST segment most likely by reducing I_{to} secondary to an increase in heart rate as well as by augmenting I_{Ca}. We found that N406 Brugada mutation changes the pharmacological response of the encoded channel in a manner that differs not only from WT but also from other Brugada mutant channels [9]. Judging from this experiment study, it might be possible that class Ib antiarrthymic drug suppresses ventricular tachycardia associated with increased ST-segment elevation in Brugada syndrome with the N406S mutant although the clinical effect of lidocaine in a patient with the N406S mutation remains unknown. The pharmacological profile of N406S channel shows distinct changes that occur over a therapeutically relevant concentration range. Our data provide further support for the usefulness of a mutation-specific pharmacological approach for the management of distinct inherited ion channel defects.

Acknowledgements

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Fig. 8. Simulation study for N406S channel. (A) Markov models for WT and N406S cardiac sodium channels. Bold lines show increased rates. A short bold line shows a decreased rate. A dotted line shows a change in voltage dependency. Simulation results for voltage-clamp protocols. The parameters used for simulation were the same as in Clancy et al. [11], except for $\alpha 13$, $\alpha 3$ and $\alpha 5$; $\alpha 13 = 3.802/(0.1027 \times \exp((-v+8)/9) + 0.25 \times \exp(-v/150))$, $\alpha 3 = 2.5 \times 3.7933 \times 10^{-7} \times \exp(-v/7.7)$, $\alpha 5 = 2 \times \alpha 2/(9.5 \times 10^4)$, $\beta 5 = \alpha 3/3000$. Some parameters including $\beta 2$ and $\beta 4$ were indirectly modified. (B-a) The peak current–voltage relationship. The potential of the maximum peak current amplitude of N406S was more positive to that of WT. (B-b) The voltage dependence of steady-state activation of N406S was positively shifted, and the slope factor was larger. The voltage dependence of steady-state inactivation of N406S was shifted towards more positive potentials. (B-c and -d) The time course of recovery from fast and intermediate inactivation. The N406S channel had faster recovery from the fast inactivation than WT. On the other hand, double-exponential fitting revealed that N406S had a larger time constant for the slow recovery component than WT. We could reproduce the slower recovery of N406S from intermediate inactivation when the equilibrium point between IM1 and IM2 was shifted toward IM2. The parameters used for simulation were the same as in Clancy et al. [11], except for $\alpha 13$, $\alpha 3$, $\alpha 5$ and $\beta 5$. The parameters $\beta 2$ and $\beta 4$ were indirectly modified [1].

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Circ J 2007; **Suppl A:** A-50–A-53

Disorders of Cardiac Repolarization
— Long QT and Short QT Syndromes —

Minoru Horie, MD, PhD; Hideki Itoh, MD, PhD

The long and short QT syndromes are heterogeneous diseases characterized by abnormal ventricular repolarization and episodes of syncope and/or life-threatening cardiac arrhythmias. Several disease-causing genes have been identified, including those encoding cardiac ion channel-composing proteins. The clinical determination of genotype offers a striking benefit: diagnosis, prediction of clinical phenotype, risk stratification, clinical and genetic counseling, and introduction of therapy. Genetic testing is of special importance for the genotyped patient's family members to prevent unexpected cardiac death. By means of recently advanced methodology in molecular genetics and electrophysiology it is expected that novel genes responsible for these disease entities will be identified. (*Circ J* 2007; **Suppl A:** A-50–A-53)

Key Words: Long QT syndrome; Short QT syndrome

The long QT syndrome (LQTS) is a primary electrical disease characterized by an abnormality in myocardial repolarization that leads to the prolongation of QT interval, morphological changes in T waves and torsades de pointes type of ventricular tachycardia on the surface ECG (Fig 1)[1,2] The association between prolongation of the QT interval and cardiac sudden death was implicated soon after the introduction of ECG recording in the clinical setting[3] In contrast, the short QT syndrome (SQTS) has been ignored for a long time and the first report relating short QT interval with an increased risk for ventricular fibrillation and cardiac sudden death appeared in 2000[4]

In the late 1990s, the advent of the molecular genetic era provided new insights into the mechanisms underlying LQTS, showing that mutations in genes encoding ion channels or their accessory proteins and other membrane proteins cause the disease. These genetic variants alter the function of ion channels governing the repolarization process of the ventricle. To date, 10 distinct genes responsible for LQTS have been identified, including those for Andersen (LQT7) and Timothy (LQT8) syndromes on chromosomes 11q15.5 (*KCNQ1*; LQT1), 7q35-36 (*KCNH2*; LQT2), 3p21 (*SCN5A*; LQT3), 4q25-27 (*ANKB*; LQT4), 21q22 (*KCNE1*; LQT5), 21q22 (*KCNE2*; LQT6), 17q23 (*KCNJ2*; LQT7), 12p13.3 (*CACN1c*; LQT8), 3p25 (CAV3; LQT9) and 11q23.3 (*SCN4B*; LQT10)[5–13] (Table 1).

In 2004, Brugada et al[14] reported the first mutation associated with SQTS. It was a *KCNH2* mutation, N588K, involving a substitution of lysine for asparagine in position 588 of *KCNH2*. Since then 3 disease-causing genes for SQTS have been identified, including genes encoding cardiac ion channel-composing proteins on chromosomes 7q35-36 (*KCNH2*; SQT1),[14] 11q15.5 (*KCNQ1*; SQT2),[15,16] and 17q23 (*KCNJ2*; SQT3)[17] (Table 2).

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LQTS

The estimated prevalence of LQTS in the general population is 1 in 5,000![18] During an ECG checkup of Japanese school pupils, its prevalence was 1 in 1,200![19] The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression[20] LQTS has played a key role as a "Rosetta Stone" in the understanding of the general mechanism of ion channel disease. Fig 2 is a schematic explanation of how a functional alteration in ion channels causes prolongation or abbreviation of the QT intervals on ECG. Electrophysiological assays using a heterologous expression system have shown that some mutations in the aforementioned genes induce a gain or loss-of-function in a respective ion channel and thereby modulate the repolarization process. For example, a reduction in outward K channel currents or an increase in the inward Na^+ or Ca^{2+} channel currents would delay repolarization of the action potential, and therefore prolong the QT interval on the surface ECG.

Now that we know most of the genes responsible for repolarization disorder and the resultant clinical phenotypes, molecular testing for mutation screening of disease genes has become feasible. The availability of genetic testing offers the possibility of identifying genetically affected individuals who are, in other words, potential victims of cardiac sudden death. The clinical determination of genotype offers a striking benefit, including diagnosis (family screening and preclinical diagnosis), prediction of clinical phenotype (penetrance, gene-specific clinical manifestations[21]), risk stratification (assessment of malignant vs benign mutations[22]), clinical and genetic counseling (restriction of physical activity, family planning etc), and therapy (prevention of sudden death by implantable defibrillator (ICD)).

One of the most important aims of genetic testing is to achieve a preclinical diagnosis of LQTS, particularly in family members with incomplete disease expression[20] or in patients with a *forme fruste* phenotype[23,24] Molecular genetic examination does strengthen the clinically overt or suspicious diagnosis. However, the genetic variant identified in

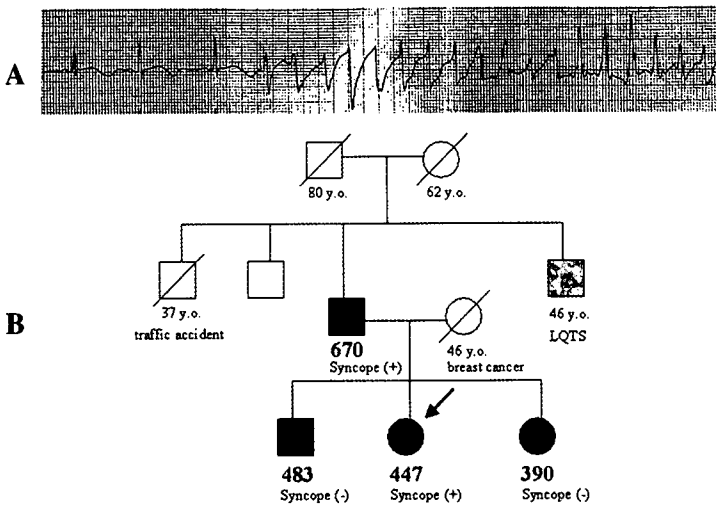

Fig 1. Distinctive ECG features and family tree associated with long QT syndrome (LQTS). (A) Torsades de pointes type of ventricular tachycardia in a patient with genotyped LQT2. Torsade de pointes frequently appeared during sleep. (B) Family analysis associated with the patient. The proband (arrow) was diagnosed as LQT2 with the G572S mutation, which is located in the S5-pore site for the KCNH2 channel. Heterozygous mutation carriers are indicated by filled symbols, and the numbers below the symbols are the QTc interval at rest. Although the index patient and her father, both carrying the G572S mutation, had syncope at rest, the other 2 mutation carriers remained asymptomatic. The proband had 2 uncles, 1 of whom (open symbol) was genetically negative, and the other (halftone filled) was clinically LQTS, although the genetic data were not available.

Table 1 Gentic Classfication of LQTS

Subtypes	*Genetic locus*	*Genes*	*Ion channel*
Congenital LQTS (Romano-Ward syndrome)			
LQT1	*11 (11p 15.5)*	*KCNQ1*	I_{Ks}
LQT2	*7 (7q 35-36)*	*KCNH2*	I_{Kr}
LQT3	*3 (3p 21-24)*	*SCN5A*	I_{Na}
LQT4	*4 (4q 25-27)*	*Ankyrin-B*	$[Ca^{2+}]i$
LQT5	*21 (21q 22.1-q22.2)*	*KCNE1*	I_{Ks}
LQT6	*21 (21q 22.1-q22.2)*	*KCNE2*	I_{Kr}
LQT7	*17 (17q 23)*	*KCNJ2*	I_{K1}
LQT8	*12p 13.3*	*CACNA1C*	$I_{Ca\text{-}L}$
LQT9	*3 (3p 25)*	*CAV3*	I_{Na}
LQT10	*11q 23.3*	*SCN4B*	I_{Na}
Congenital LQTS (Jervell and Lange-Nielsen syndrome)			
JLN1	*11 (11p 15.5)*	*KCNQ1 (homozygous)*	I_{Ks}
JLN2	*21 (21q 22.1-q22.2)*	*KCNE1 (homozygous)*	I_{Ks}

LQTS, long QT syndrome.

Table 2 Gentic Classfication of SQTS

Subtype	*Gene*	*Mutations*	*QTc*	*Functions*	*Reference*
SQT1	*KCNH2*	*N588K*	*286*	*Impaired inactivation of I_{Kr}*	*14*
SQT2	*KCNQ1*	*V141M*	*AF*	*Accelerated activation of I_{Ks} Hyperpolarized shift of the activation curve*	*15*
		V307L	*302*	*Faster activation*	*16*
SQT3	*KCNJ2*	*D172N*	*315*	*Larger I_{K1} currents*	*17*
SQT4	*CACNB2b*	*S481L*	*330–370*	*loss-of-function in L-type Ca channel Brugada phenotype*	*39*
SQT5	*CACNA1C*	*A39V G490R*	*346–360*	*loss-of-function in L-type Ca channel Brugada phenotype*	*39*

SQTS, short QT syndrome; AF, atrial fibrillation.

an individual does not directly explain the clinical phenotypes. Mutation carriers may have either no disease phenotype (incomplete penetrance) or present with various degree of clinical manifestations, ranging from asymptomatic with relatively prolonged QT interval and no arrhythmias to those experiencing cardiac arrest even under β-blocker therapy or after ICD implantation. Thus, inheriting a mutation does not always mean that the individual will present a clinical manifestation of LQTS, but apparently "healthy" mutation carriers have inherited the risk for developing the clinical phenotype. Because congenital LQTS affects the young, all efforts should be made to genotype them for appropriate management of both the patient and the family members who may be at highest risk of sudden death. These efforts are justified by timely therapy with β-blockers and/or ICD in association with careful clinical follow-up to avoid hypokalemia, bradycardia and drugs that prolong the QT interval[25–27] and family education, including the use of an automated electrical defibrillator at home.

Through the elucidation of pathophysiological mechanisms underlying the congenital LQTS during the past decade, we have witnessed the most rapid and fruitful progress in powerful scientific tools: molecular genetics and cellular physiology. We are expecting to identify novel additional genes responsible for the disease.

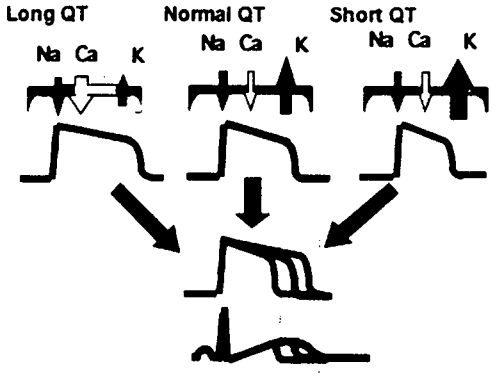

Fig 2. Schematic presentation of ion currents governing the action potential duration in the ventricle. Action potential duration (APD) varies depending on the subtle balance between inward and outward currents. An increase in the inward Na^+ and Ca^{2+} currents (blue and yellow arrows) or a decrease in the outward K^+ current (red arrow) prolongs the APD and causing long QT syndrome (Left panel). Conversely, an increase in the outward K^+ currents shortens the APD, causing short QT syndrome (Right panel).

SQTS

SQTS constitutes a new primary electrical abnormality associated with sudden cardiac death[4,28] The family first reported by Gussak et al[4] consisted of patients with a constantly-shortened QT interval and paroxysmal atrial fibrillation, and one member had died of sudden cardiac death[28] Subsequently, the short QT interval was shown to be associated with sudden cardiac death without structural heart disease![4–17] The syndrome is now considered as a new cardiac ion channel disease![11,28–32]

The diagnostic criteria for SQTS currently include (1) QTc interval <330 ms, (2) ventricular tachycardia without structural heart disease, and (3) a family history of sudden cardiac death[33] Atrial fibrillation is a characteristic complication[4,15,33] and Giustetto et al[34] demonstrated that 31% of patients with this syndrome had documented atrial fibrillation, even in young subjects. His group also reported that SQTS could be related to death in early infancy[34] Alhough arrhythmogenic triggers in SQTS are incompletely understood, bradycardia may predispose to ventricular tachycardia because the shortened QT interval would become obvious at a lower heart rate[33] The induction rate of ventricular tachycardia during electrophysiological examination is apparently very high in SQTS patients[33] but the issue remains unclear because information is still limited.

Three responsible genes have been reported to date (Table 2), indicating that SQTS has a genetically heterogeneous background. Brugada et al[14] identified the first missense mutation in *KCNH2*, N588K, which causes a substitution of lysine for asparagines in position 588 located in the S5-pore loop (SQTS type 1, SQT1). *KCNH2* is known as the gene responsible for LQT2, but in contrast to the case in LQTS, N588K in SQTS was found to cause a remarkable gain-of-function in I_{Kr}.

The second mutation in SQTS was found in *KCNQ1*, which encodes the slow component of the delayed rectifier potassium channel (I_{Ks}) (SQTS type 2, SQT2)![16] *KCNQ1* is also a gene responsible for LQTS (LQT1). A missense mutation (V307L) was identified in an index patient with short QT interval and ventricular fibrillation, and it causes a substitution of leucine for valine in position 307 of the *KCNQ1* pore site. Another missense *KCNQ1* mutation (V141M) was found in a baby with both shortened QT interval and atrial fibrillation![15]

The latest mutation in SQTS was identified in *KCNJ2* (type 3, SQT3)![17] Again, *KCNJ2* is responsible for Andersen syndrome (LQT7), encoding the inward rectifier K channel (I_{K1}). The missense *KCNJ2* mutation (D172N), causing a substitution of aspartic acid for asparagine in position 172, was shown to induce a gain-of-function of I_{K1}. Surface ECG features differ among the 3 subtypes of SQTS. In fact, the T wave in SQT3 associated with the *KCNJ2* mutation is asymmetrical, with a remarkably rapid terminal phase![17]

All genetic mutations in SQTS cause a gain of the outward K currents governing the ventricular repolarization, and therefore shortening the QT interval (Table 2). However, the mechanism of inducing the "gain-of-function" differs: (1) impaired inactivation in SQT1![4,35] (2) accelerated activation and hyperpolazized shift of the activation curve[15] or faster activation[16] in SQT2, and (3) larger outward currents and depolarized shift of the peak current in SQT3![17]

Regarding the arrhythmogeneity in SQTS, Antzelevitch et al have presented the first experimental evidence for the role of transmural dispersion of repolarization (TDR)[36] They used a pharmacological method with pinacidil, a strong activator of the cardiac ATP-sensitive K channel ($I_{K\text{-}ATP}$), to mimic a "gain-of-function" in outward K currents in a canine arterially-perfused wedge preparation. Pinacidil caused a heterogeneous abbreviation of the action potential duration in 3 principal cell types spanning the ventricular wall, indicating that TDR could lead to an increased vulnerability to polymorphic ventricular tachycardia.

ICD implantation is the first-line therapy for SQTS patients[37] Quinidine can prolong the QT interval and protect against ventricular fibrillation in SQT1 by suppressing I_{Kr}, whereas class Ic and III antiarrhythmic drugs (eg, flecainide, sotalol, and ibutilide) are ineffective against ventricular fibrillation[38]

Clinical information on SQTS remains scarce because the patients are very rare compared with those with LQTS. However, there is no doubt that SQTS is strongly associated with an abnormality of the genes encoding cardiac ion channels. Strategies used in the study of LQTS would therefore be useful for further clarification of SQTS.

Note:

After submitting the manuscript, a report on novel mutations causative of SQTS appeared regarding cardiac L-type Ca channel genes: *CACNB2b* and *CACNA1C* encoding α_1 and β_{2b} subunits of Ca channel[39] (SQT 4 and 5 in Table 2). Functional analyses revealed that 2 mutations of *CACNA1C* (A39V and G490R) and one *CACNB2b* (S481L) caused a loss-of-function in Ca channel currents. The probands' phenotypes carrying these mutations of Ca channel genes were characterized by cardiac sudden death, atrial fibrillation and Brugada type ECG patterns.

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Association of Atrial Arrhythmia and Sinus Node Dysfunction in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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Background This study was performed to investigate the frequency and importance of supraventricular arrhythmia and sinus node (SN) dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

Methods and Results Eight patients with CPVT (mean age: 16.8±8.1 years) underwent an electrophysiological study. SN recovery time (1,389±394 ms) was slightly prolonged, and 4 of 8 patients had abnormal values. Atrial flutter (AF) was induced by low-rate atrial pacing in 2 patients and by isoproterenol infusion in 1 patient. Atrial fibrillation (Af) was induced by isoproterenol infusion in 2 patients. One patient presented with Af during the follow-up period, and 2 of 4 patients with AF/Af presented with increased SN recovery time.

Conclusions Patients with CPVT frequently have associated with SN dysfunction, and inducible atrial tachyarrhythmias, which indicate that the pathogenesis of CPVT is limited not only to the ventricular myocardium, but also to broad regions of the heart, including the SN and atrial muscle. (*Circ J* 2007; **71:** 1606–1609)

Key Words: Atrial fibrillation; Delayed afterdepolarization; Sinus node dysfunction; Ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by the development of bidirectional ventricular tachycardia (VT) or polymorphic VT induced by exercise or emotional stress in children and young adults[1–11] Mutations in the ryanodine 2 receptor (*RyR2*) gene[12–15] and calsequestrin 2 (*CASQ2*) gene[14,16–18] have been identified in patients with CPVT, and triggered activity because of delayed afterdepolarization is thought to be the underlying cellular mechanism of the arrhythmias[19]

Although the clinical characteristics of patients with CPVT are well defined, atrial arrhythmias and sinus node (SN) function have not been evaluated in previously published studies. This study was performed to investigate frequency and importance of supraventricular arrhythmia and SN dysfunction in patients with CPVT.

Methods

The diagnosis of CPVT was made according to our criteria described in a previous report[11] Eight patients (7 females, 1 male) who were referred for evaluation of arrhythmias were studied (mean age 16.8±8.1 years; range: 9–37 years). One patient (patient no. 1) underwent an electrophysiologic study (EPS) twice for reevaluation of medical treatment (Table 1). This patient had mild pulmonary stenosis with a pressure gradient of 10 mmHg between the main pulmonary artery and right ventricle. Patient nos. 5 and 6 are sisters discovered by familial screening.

These patients underwent EPS in the fasted state after written informed consent was given by either the patient or their parents. Quadripolar electrode catheters were positioned in the right ventricle, high right atrium, and septal leaflet of the tricuspid valve to record electrocardiograms (ECGs) and to pace the right atrium and right ventricle.

Programmed right atrial and ventricular stimulation was performed to induce atrial arrhythmia, VT or ventricular fibrillation (VF). SN function and atrioventricular conduction properties were also studied.

Genetic analysis of the ryanodine receptor was performed in 6 patients (patient nos. 2,4,5–8). In September 2001 the ethical committee of Nihon University School of Medicine approved analysis of the entire genome and of the gene for the life-threatening arrhythmia. Two of the patients did not undergo genetic analysis because 1 died (no. 1) and the other patient's parents (patient no. 3) refused.

Statistical Analysis

All numeric data are presented as the means±SD. Because of differences in the variables and limited sample numbers, statistic analysis was performed using Wilcoxon nonparametric analysis or chi-square analysis when necessary. A p-value less than 0.05 was considered significant.

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Table 1 Patients' Demographics and Basic Electrophysiologic Data

Patient no.	Age (years)	Sex	Onset	AH	HV	RA-ERP	AVN-ERP	W rate	SNRT	cSNRT
1	13	F	Syncope	70	40	230	310	190	1,430	695
	24			76	26	230	250	160	1,617	785
2	11	F	Syncope	96	55	270	315	180	1,316	407
3	15	F	Syncope	70	40	210	410	180	1,930	930
4	37	F	Syncope	95	35	290	320	140	1,305	440
5	9	F	Familial	60	35	285	300	170	890	190
6	11	F	Familial	60	35	275	285	200	760	155
7	13	M	Syncope	62	44	210	264	200	1,248	552
8	15	F	Syncope	85	38	210	530	100	2,002	889

AH, AH interval; HV, HV interval; RA-ERP, high-right-atrium effective refractory period; AVN-ERP, atrioventricular nodal effective refractory period; W rate, Wenckebach rate; SNRT, sinus node recovery time; cSNRT, corrected sinus node recovery time.

Results

Patient Characteristics

Table 1 presents the demographic and basic electrophysiologic data for the 8 patients. The presenting symptom of CPVT was syncope in 6 patients (75%), and 2 patients (25%) had a family history (patient nos. 5 and 6). One of the familial patients experienced syncope during the follow-up period (patient no. 5). Clinically, polymorphic VT (patient nos. 3,5,6,8), polymorphic VT and bidirectional VT (patient nos. 2 and 4), polymorphic VT and VF (patient no. 1), and bidirectional VT (patient no. 7) were documented. VT and VF were not induced by programmed ventricular stimulation in any patient.

Only 1 patient (patient no. 2) had a missense mutation of *RyR2* (A7420G).

Resting Electrophysiological Data

The sinus cycle length (834±111 ms), AH interval (75±13 ms) and HV interval (39±8 ms) were within normal limits. The right atrial effective refractory period was 246±32 ms, and the atrioventricular nodal effective refractory period was 332±82 ms. The Wenckebach rate of atrioventricular conduction was 169±30 beats/min, while 1 patient had a prolonged atrioventricular nodal effective refractory period (530 ms), with a decreased Wenckebach rate of 100 beats/min. The right ventricular effective refractory period was normal in all of the patients with a mean value of 254±49 ms. The SN recovery time (SNRT) and corrected SNRT (cSNRT) were slightly prolonged (1,389±394 ms and 560±286 ms, respectively). The SNRT exceeded 1,400 ms in 3 patients, and the cSNRT exceeded 525 ms in 4 patients, and 3 of 4 patients have prolongation of both SNRT and cSNRT.

Atrial Arrhythmias

Atrial arrhythmias were noted clinically in 3 patients (patient nos. 1,2,4), and were induced during electrophysiologic testing in 3 patients (patient nos. 1–3) (Table 2). Atrial flutter (Af) was induced by programmed atrial stimulation in 2 patients (patient nos. 1 and 3).

Patient no. 1 had documented sustained Af immediately after she was resuscitated from VF and sustained Af was also induced by relatively low-rate atrial burst pacing at 160 beats/min. Her SNRT and cSNRT were prolonged to 1,617 ms and 785 ms, respectively.

Atrial fibrillation (AF) was induced by infusion of isoproterenol (ISP) in patient no. 2. As shown in Fig 1, the bidirectional VT induced by ISP was overdriven by a rapid ventricular response following induced AF. This patient's SNRT and cSNRT were normal. Frequent episodes of paroxysmal AF were documented during walking or with mental stress.

Table 2 Atrial Arrhythmia Induction

Patient no.	Atrial arrhythmia		
	Clinical	PAS	ISP
1	AFL	AFL	NI
2	AF	NI	AF
3	None	AFL, AF	NI
4	AF	NI	NI
5	None	NI	NI
6	None	NI	NI
7	None	NI	NI
8	None	NI	NI

PAS, programmed atrial stimulation; ISP, isoproterenol; AFL, atrial flutter; NI, not induced; AF, atrial fibrillation.

Sustained atrial tachyarrhythmias (Af/AF) were induced by burst atrial pacing at 100 beats/min or programmed atrial pacing in patient 3. This patient's SNRT and cSNRT were prolonged to 1,930 ms and 930 ms, respectively. Af/AF were induced by ISP infusion. Patient no. 4 presented with frequent attacks of paroxysmal AF during the follow-up period. In the Af/AF group (patient nos. 1–4), 2 patients showed prolonged SNRT and cSNRT.

The SNRTs were compared between the Af/AF group (patient nos. 1–4) and the group without Af/AF (patient nos. 5–8). The Af/AF group had a longer SNRT (1,542±296 ms) and cSNRT (641±258 ms) than the group without Af/AF (1,225±558 ms and 446±345 ms, respectively), although the difference was not statistically significant.

Discussion

Patients with CPVT have been reported to have a poor prognosis because of ventricular tachyarrhythmias and because sometimes the risk of sudden cardiac death cannot be reduced despite maximal medication. Ventricular tachyarrhythmias seen in CPVT are characterized by the unique ECG manifestations of bidirectional VT, polymorphic VT and/or VF[1-11] The clinical characteristics of the ventricular tachyarrhythmias and their possible role in syncope and sudden cardiac death in patients with CPVT have been described. Although, sinus bradycardia[7,11,20] and atrial arrhythmia (junctional rhythm and AF)[7] have been noted, the electrophysiologic characteristics of SN and atrioventricular node function, and the risk of development of atrial

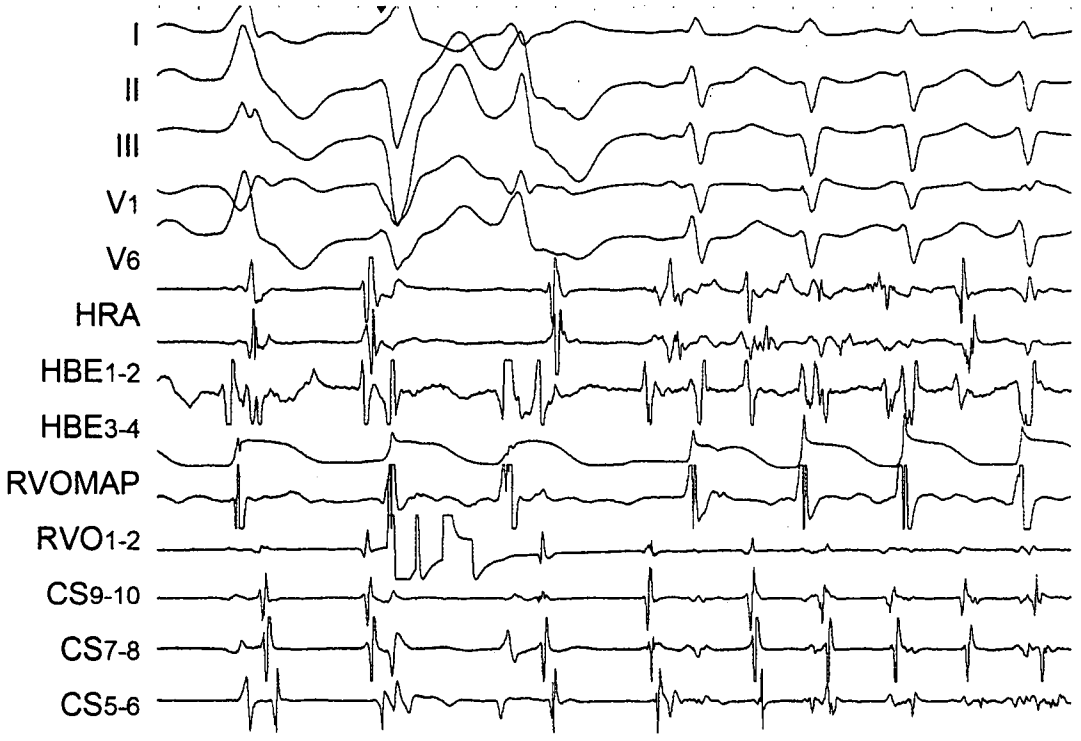

Fig 1. Atrial fibrillation induction by isoproterenol. Electrocardiogram (ECG) from an 11-year-old girl (patient no. 2) with catecholaminergic polymorphic ventricular tachycardia. Infusion of 0.66μg/min of isoproterenol induced bidirectional ventricular tachycardia, which was converted to atrial fibrillation. I, surface ECG lead I; II, lead II; III, lead III; V_1, lead V_1; V_6, lead V_6; HRA, high right atrium; HBE, His bundle ECG; RVOMAP, right ventricular outflow monophasic action potential; RVO, right ventricular outflow; CS, coronary sinus.

arrhythmias, have not been well studied. Our study clearly demonstrates that SN and atrioventricular node function are both impaired in some of these patients and that there is a common association with spontaneous or exercise/catecholomine-induced Af/AF, suggesting that the background arrhythmogenic substrate of this disease involves the supraventricular tissues, as well as the ventricle.

Pathogenesis of CPVT

With respect to the pathogenesis of CPVT, mutations of *RyR2* in autosomal dominant inheritance[10,12,13] and *CASQ2* in autosomal recessive forms[14] have been described. Therefore, the incidences in the latter are thought to be very low and most of the present patients are assumed to have the former mutation. *RyR2* encodes the Ca^{2+} release channel of the sarcoplasmic reticulum membrane, which plays an essential role in the Ca^{2+}-induced Ca^{2+} release (CICR) in cardiac cells. Mutations of *RyR2* are thought to increase CICR at rest or increase the sensitivity to caffeine and adrenergic stimulation. Increased CICR could induce Ca^{2+}-overload of myocardial cells, leading to the development of delayed afterdepolarization, similar to digitalis intoxication. Triggered activity caused by delayed afterdepolarization is thought to be the cellular mechanism responsible for arrhythmias in CPVT.

Atrial Arrhythmias and CPVT

In the present study, atrial arrhythmias were observed in a number of CPVT patients (3–19%). Inappropriate ICD discharges are sometimes delivered in patient with CPVT with AF. There are, however, no reports concerning the development of atrial tachyarrhythmias, especially AF, in CPVT patients. Our study suggests that patients with CPVT have frequent SN dysfunction, disturbances in atrioventricular nodal conduction, and inducible atrial tachyarrhythmias. Therefore, ICD implantation in CPVT patients requires careful follow-up for inappropriate ICD discharge, because of the development of AF. This suggests that the pathogenesis of CPVT involves not only the ventricular myocardium, but also broad regions of the heart including the SN, atrial muscle, and atrioventricular node.

Recently, Masumiya et al[21] have identified *RyR2* and *RyR3* in the SN. Rhythmic intracellular ryanodine receptor Ca^{2+} release regulates the activity of pacemaker cells, which do not require preceding membrane depolarization during diastolic depolarization[22] However, Honjo et al[23] claim that sarcoplasmic reticulum Ca^{2+} release is not a predominant factor in the pacemaker activity of SN cells. High basal cAMP content in SN cells can increase protein kinase A-dependent phosphorylation, resulting in spontaneous beating[24] Although a dominant role for the *RyR2* channel in normal pacemaker activity is still a matter of debate, Ca^{2+} release through the ryanodine receptor and its modulation by protein kinase A-dependent phosphorylation may influence the pacemaker function of the SN. Therefore, we speculate that spontaneous sarcoplasmic reticulum Ca^{2+} cycling is not performed smoothly in the SN cells because of the *RyR2* channel dysfunction, which results in SN dysfunction as well as atrial tachyarrhythmias because of the decrease and/or loss of dominant pacemaker function in the SN and atrial Ca^{2+} overload similar to that seen in ventricular cells. The impaired function of the atrioventricular node cells may also be explained by Ca^{2+} overload in a similar way as occurs in ventricular cells in CPVT.

Study Limitations

Because the number of patients with CPVT was extremely small, the electrophysiologic findings from them were limited. Also, the SNRT and sino-atrial conduction time could change with age and maturation of autonomic tone. The entire *RyR2* gene was not analyzed; only 33 of the 105 exons.

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Expertise

家族性心房細動を識る

▷*Familial atrial fibrillation*

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キーワード
イオンチャネル病，KCNQ1，KCNH2，KCNJ2

心房細動(atrial fibrillation；AF)の成因は，もちろん，大変多様であり，1つの原因説ではとうてい説明できないことは明らかである(特集1「心房細動の診断と病型」参照)。最近，AFの機序あるいは誘因に関する非常に長いリストの最後に遺伝的背景が追加された。
本稿では，あまり知られていなかった家族性AFについてイオンチャネル病としての側面からまとめる。

家族性心房細動と遺伝子異常

家族内にAFが集積する事実は，実際，以前より知られており，いくつかの症例報告がみられている[1-4]。1997年になって，Brugadaら[5]は連鎖解析法を用い，第10番染色体(10q22-24)に新たなAF関連遺伝子が存在することを報告した。異なる3家系で，幼少時からAFを呈すること，常染色体優性遺伝を示すことなどを発見したが，遺伝子そのものは同定できなかった。

その後，2003年のはじめ，Chenら[6]は，器質的な心疾患を有さない家族性AFで，4世代にわたる常染色体優性遺伝形式を示す中国人家系を詳細に検討し*KCNQ1*遺伝子の変異を発見した。*KCNQ1*はI_{Ks}を流す遅延整流Kチャネルをコードする遺伝子である。同じく*KCNQ1*遺伝子のloss-of-function型の変異は先天性QT延長症候群(LQT1)を起こすことが知られている。本家系のシークエンシングでは，*KCNQ1*蛋白の140番目のセリンがグリシンに置換するミスセンス変異(S140G)が，AF症例にのみ同定された。*KCNQ1*は，したがって，FAF1(familial atrial fibrillation)の原因遺伝子とされる。

本来，*KCNQ1*を有さない培養細胞COS7を用いた発現実験[6]では，S140G変異により再構築されるI_{Ks}は急速な

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活性化を示し，脱分極時(+20mV)には正常チャネルの約3倍の外向き電流，過分極時には内向き電流を生じた。つまりS140GはIKsの機能亢進ばかりでなく，その電気生理学的特性も変化させる異常であった(図1)。このような変化は，心房筋の活動電位持続時間(action potential duration；APD)を短縮し，さらに静止膜電位を安定化させることにより心房不応期の短縮を促し，AFの発生とその維持に好適な状況を生み出す。したがって*KCNQ1* S140Gは疾患との関連が強く疑われ，最初の遺伝性AFの原因変異とされた。

さらにこの報告を通して，

①同じ*KCNQ1*変異であっても，その招来される機能変化の方向によっては表現型がまったく変化すること(すなわち臨床像としてのAFと前述のQT延長症候群)

②ヒトAF発症にIKs増加が関与していること

③AF治療におけるIKsブロッカーの有効性も考慮されること

などが明らかとなった点である。

その後，①のQT延長症候群の反対側にある病態としての家族性AFが注目され，多くの研究者が，QT延長症候群関連遺伝子に注目して本症で検索している。2004年になって，Yangら[7]は中国人の家族性AF28家系について*KCNQ1*, *HERG*, *KCNE1*, *KCNE2*, *KCNE3*, *KCNE4*, *KCNE5*, *KCNJ2*の8関連遺伝子を調べたところ，*KCNE2*のR27Cというミスセンス変異が28人の発端者のうち2人に発見されたと報告した。

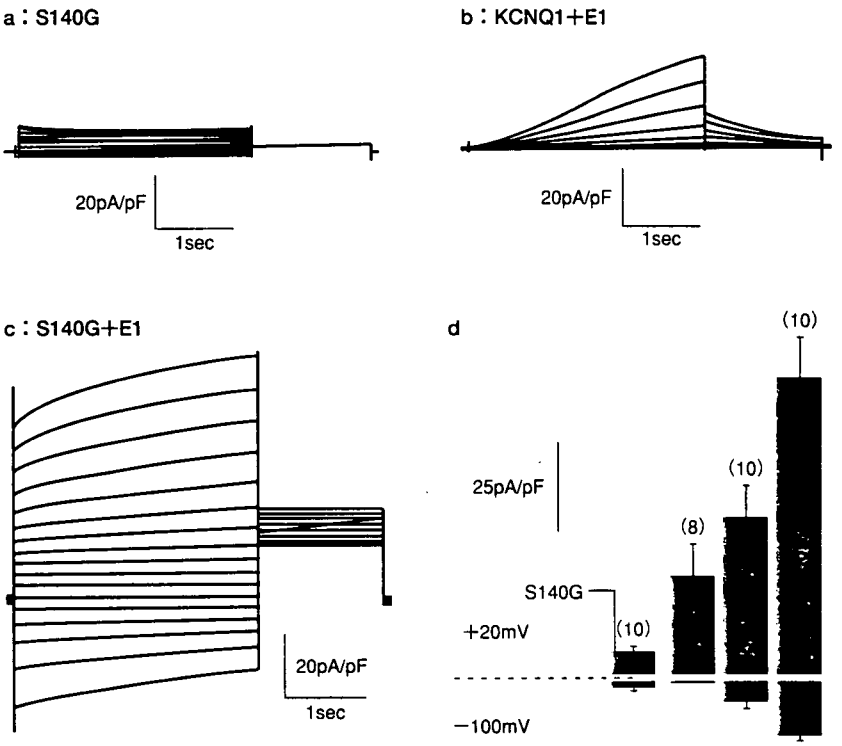

図1 本来*KCNQ1*を発現していないCOS7細胞に正常*KCNQ1*およびS140G変異を導入してパッチクランプ法でK電流を測定(文献6より引用)

aはS140G変異単独の導入で，発現量は少ないが，b，cにみられるように，βサブユニットであるKCNE1(E1と記載)と同時発現させると，S140G変異チャネルは有意に大きな電流を運ぶのみならず，不活性化ゲートが消失して，内向きにも大きな電流を運ぶことが示された。dは，多くの細胞から得られた+20mVおよび−100mVでの電流密度を棒グラフで示す。

この*KCNE2* R27C変異は，2人の発端者を含めてAFを有する家族で陽性であったのに対して，AFを有さない家族や462名のコントロールでは陰性であった。また，R27C変異は，KCNQ1-KCNE2チャネルのgain-of-functionを起こした。したがって，この変異も家族性AFに関連すると考えられ，現在，FAF2とされている。さらに，FAF3も，同じグループにより発見された。2005年に30人の家族性AFの発端者の一人に*KCNJ2*遺伝子の変異(V93I)が報告された[8]。*KCNJ2*は，LQT7と分類されるAndersen症候群やshort QT syndromeの原因遺伝子[9,10]ともされており，いわゆるoverlap症候群の可能性がある。

家族性心房細動の新しいメカニズムとしての*KCNQ1* R14C変異

冒頭で述べたように，心房細動は多因子疾患であるが，遺伝的な背景が，

その発症を後押しするという意味で，最近大変興味深い論文が発表された[11]。家族性心房細動の50家系についてQT延長症候群関連遺伝子を調べたところ，高血圧を伴う一家系で*KCNQ1* R14C変異が発見された。心房細動は，この変異のheterozygous carrierで，高齢者に限って発症していた。*KCNQ1*がコードする遅延整流Kチャネルは，細胞膜のストレッチで活性化することが知られている[12]。そこで，図2に示すように，Otwayらは，野生株の*KCNQ1*とR14C変異株を，培養細胞に導入しパッチクランプ法で電流記録しながら，低浸透圧液によるストレッチ刺激を与えたところ，野生株に比べてR14C変異では，同じレベルの刺激に対して，有意に大きな電流増加を得ることが観察された。この変異を有する家系では，高血圧症を高頻度に合併していたが，左心室のコンプライアンスが低下するような病態では，左房がストレッチ刺激を受け遅延整流Kチャネル電流のupregulationを介して心房細動が起こりやすくなる可能性が示唆された。

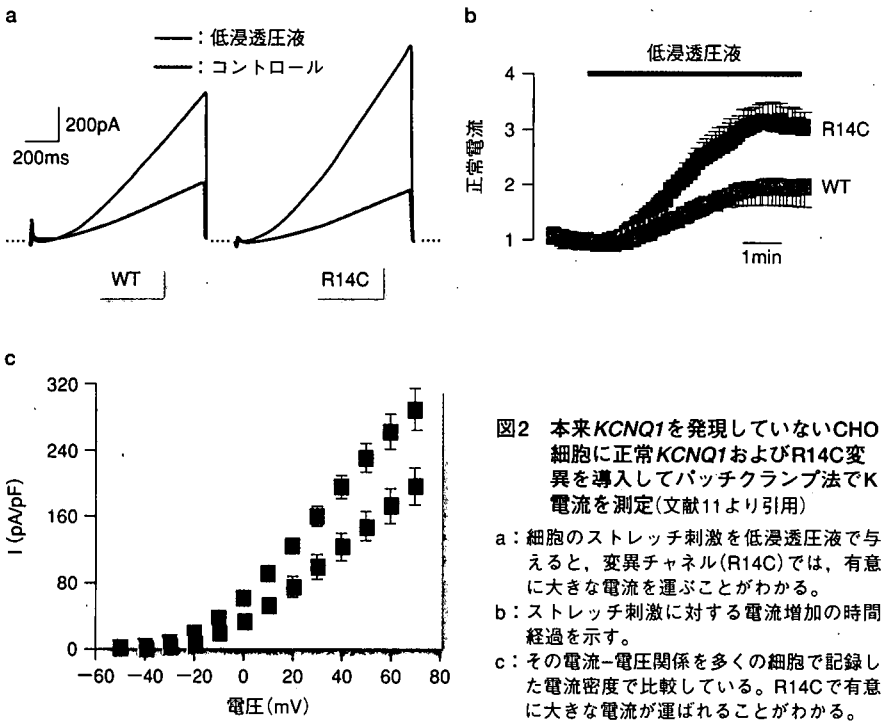

図2　本来*KCNQ1*を発現していないCHO細胞に正常*KCNQ1*およびR14C変異を導入してパッチクランプ法でK電流を測定(文献11より引用)

a：細胞のストレッチ刺激を低浸透圧液で与えると，変異チャネル(R14C)では，有意に大きな電流を運ぶことがわかる。
b：ストレッチ刺激に対する電流増加の時間経過を示す。
c：その電流−電圧関係を多くの細胞で記録した電流密度で比較している。R14Cで有意に大きな電流が運ばれることがわかる。

おわりに

心房細動の遺伝的な背景は，やっとほんの少しが解明されたところであり，また，遺伝的な因子で影響を受けるのは，一部であろうと考えられている。今後のさらなる研究の進展が待たれる。

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症　例

心筋リアノジン受容体の遺伝子変異(I4587V)を有したカテコラミン誘発性多形性心室頻拍の1成人症例

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芦原貴司* 伊藤英樹* 八尾武憲* 坂口知子*
中澤優子* 岡　優子* 辻　啓子* 堀江　稔*

症例は37歳女性．15歳時，運動中に意識消失をきたしたが放置していた．30歳頃から再び運動時や精神的ストレスに伴って数分の失神発作を起こすようになった．36歳時，悪夢で覚醒し，直後に数分の意識消失を家人に目撃されて初めて近医を受診した．基礎心疾患はなく，安静時心電図異常も認めなかったものの，ホルター心電図で心室頻拍が捉えられ，トレッドミル試験で多形性心室頻拍が出現した．電気生理検査で心室頻拍は誘発されなかった．カテコラミンの持続投与により多形性心室頻拍が誘発されたことからカテコラミン誘発性多形性心室頻拍症(CPVT)と診断した．遺伝子検索ではリアノジン受容体(*RYR2*)の膜貫通領域である4587番目のアミノ酸がイソロイシンからバリンに置換されるミスセンス変異を認めた．β遮断薬の内服では心室頻拍は完全には抑制されず，徐脈と低血圧を生じたため植込み型除細動器移植術を行った．　(心電図，2007；27：246～252)

Keywords
- 心室頻拍
- カテコラミン誘発性多形性心室頻拍
- リアノジン受容体
- β遮断薬
- 植込み型除細動器

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Ⅰ．はじめに

カテコラミン誘発性多形性心室頻拍症(catecholaminergic polymorphic ventricular tachycardia：CPVT)は精神的ストレスや運動により誘発される双方向性(bidirectional)もしくは多源性の心室頻拍を起こすまれな遺伝性不整脈疾患であり，QT延長症候群やBrugada症候群などと同様に心臓突然死を引き起こす原因疾患の一つと考えられ

A novel missense mutation in the human cardiac ryanodine receptor gene (I4587V) *in a patient with catecholaminergic polymorphic ventricular tachycardia*
Kenichi Dochi, Yuichi Matsumoto, Iori Nagaoka, Makoto Ito, Takashi Ashihara, Hideki Ito, Takenori Yao, Tomoko Sakaguchi, Yuko Nakazawa, Yuko Oka, Keiko Tsuji, Minoru Horie

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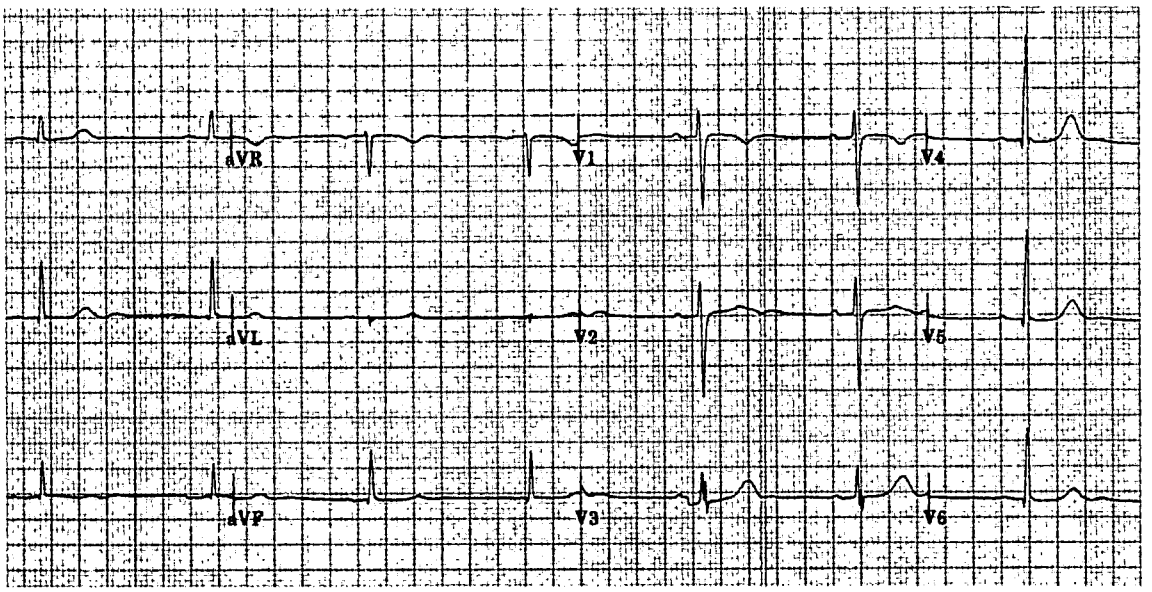

図1　入院時，安静12誘導心電図

ている[1)~4)]．また多くは器質的に異常のない心臓で小児期に発症するが成人でも突然死を引き起こすとされている．CPVTに対する治療にはβ遮断薬が用いられることが多いが無効例も多くβ遮断薬内服下の39例中18例で心室性頻拍の再発が認められ，ICD移植の必要な症例は30％という報告もある[1)]．最近，CPVTの原因として心筋細胞内の筋小胞体に存在しカルシウム放出を制御しているリアノジン受容体(*RyR2*)や，カルシウム結合蛋白であるcarsequestrin(*CASQ2*)の遺伝子異常が報告されている[5)~10)]．これまでに，リアノジン受容体には62個の遺伝子変異が報告されており常染色体優性の遺伝形式をとるとされる．一方，carsequestrinによる遺伝子異常は常染色体劣性の遺伝形式をとりこれまでに4個の遺伝子変異が報告されている．今回，リアノジン受容体の膜貫通領域に遺伝子変異がみつかり，またβ遮断薬が無効でICD植込みを必要とした症例を経験したので報告する．

Ⅱ．症　　例

症例：37歳，女性

主訴：失神発作

既往歴：特になし

家族歴：突然死，心疾患等なし

現病歴：15歳時，短距離走や水泳中に意識が消失したことがある．しかし，その後，失神はなかった．30歳時，自転車にて登坂中およびバイクとの接触事故による感情ストレスの際に失神をきたした．36歳時，夜間悪夢にて覚醒した直後の失神発作を家人に目撃されたことで近医受診した．近医の運動負荷心電図にて双方向性心室頻拍が認められた．β遮断薬(アテノロール50 mg)の内服を開始したが心室性頻拍は抑制されず，徐脈と低血圧を生じたためカルベジロール5 mgに変更された．その後，失神発作は年に一回程度に抑制されていた．しかし運動負荷で心室頻拍が認められたため，入院となった．

入院時現症：身長164 cm，体重51 kg，脈拍46/分，血圧118/68 mmHg，心音は異常なし，心雑音認めず．下腿浮腫なし．安静12誘導心電図は心拍数50/分の洞性徐脈で，QT時間は0.4秒，QTcは0.423秒と正常範囲であった(図1)．胸部X線写真では心胸郭比は48％，心陰影は正常．心臓超音波検査では左右心室の壁運動は正常，心房心室腔の拡大はともに認めなかった．