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# Clinical Aspects of Type-1 Long-QT Syndrome by Location, Coding Type, and Biophysical Function of Mutations Involving the KCNQ1 Gene

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**Background**—Type-1 long-QT syndrome (LQTS) is caused by loss-of-function mutations in the KCNQ1-encoded  $I_{Ks}$  cardiac potassium channel. We evaluated the effect of location, coding type, and biophysical function of KCNQ1 mutations on the clinical phenotype of this disorder.

**Methods and Results**—We investigated the clinical course in 600 patients with 77 different KCNQ1 mutations in 101 proband-identified families derived from the US portion of the International LQTS Registry (n=425), the Netherlands' LQTS Registry (n=93), and the Japanese LQTS Registry (n=82). The Cox proportional hazards survivorship model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of time-dependent cardiac events from birth through age 40 years. The clinical characteristics, distribution of mutations, and overall outcome event rates were similar in patients enrolled from the 3 geographic regions. Biophysical function of the mutations was categorized according to dominant-negative (>50%) or haploinsufficiency ( $\leq$ 50%) reduction in cardiac repolarizing  $I_{Ks}$  potassium channel current. Patients with transmembrane versus C-terminus mutations (hazard ratio, 2.06;  $P<0.001$ ) and those with mutations having dominant-negative versus haploinsufficiency ion channel effects (hazard ratio, 2.26;  $P<0.001$ ) were at increased risk for cardiac events, and these genetic risks were independent of traditional clinical risk factors.

**Conclusions**—This genotype–phenotype study indicates that in type-1 LQTS, mutations located in the transmembrane portion of the ion channel protein and the degree of ion channel dysfunction caused by the mutations are important independent risk factors influencing the clinical course of this disorder. (*Circulation*. 2007;115:2481-2489.)

**Key Words:** electrocardiography ■ genetics ■ long-QT syndrome

The hereditary long-QT syndrome (LQTS) is characterized by prolonged ventricular repolarization on the ECG and arrhythmia-related syncope and sudden death.<sup>1</sup> Mutations in 1 or more of several ion channel genes are known to cause this disorder,<sup>2</sup> with mutations in the KCNQ1 gene causing the type-1 long-QT syndrome.<sup>3,4</sup> The KCNQ1 gene codes for the potassium channel protein responsible for the slow component of the delayed rectifier repolarizing current ( $I_{Ks}$ ). Mutations involving this gene result in reduction of the repolarizing  $I_{Ks}$  current and lengthening of the QT interval.<sup>3</sup>

## Clinical Perspective p 2489

Functional  $I_{Ks}$  channels result from the coassembly of 4 subunits into a tetrameric protein channel that is transported to the myocyte membrane. Each subunit contains 6 membrane-spanning domains (S1 to S6) flanked by amino (N)- and carboxyl (C)-terminus regions. Two distinct biophysical mechanisms mediate the reduced  $I_{Ks}$  current in patients with KCNQ1 mutations: (1) coassembly or trafficking defects in which mutant subunits are not transported

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properly to the cell membrane and fail to incorporate into the tetrameric channel, with the net effect being a  $\leq 50\%$  reduction in channel function (haploinsufficiency)<sup>5</sup>; and (2) formation of defective channels involving mutant subunits with the altered channel protein transported to the cell membrane, resulting in a dysfunctional channel having  $>50\%$  reduction in channel current (dominant-negative effect).<sup>6</sup>

Limited prior studies involving relatively small numbers of patients with type-1 LQTS have been reported with conflicting results on the relationship between various KCNQ1 mutations and the clinical outcome.<sup>7,8</sup> We hypothesized that the location, coding type, and functional effect of the channel mutation would have important influence on the phenotypic manifestations and clinical course of patients with this disorder. To test this hypothesis, we investigated the clinical aspects of a large cohort of subjects having a spectrum of KCNQ1 mutations categorized by their location, coding type, and type of biophysical ion channel dysfunction.

## Methods

### Study Population

The study population of 600 subjects with genetically confirmed KCNQ1 mutations was derived from 101 proband-identified families with the type-1 LQTS disorder. The proband in each family had QTc prolongation not due to a known cause. The subjects were drawn from the US portion of the International LQTS Registry (n=425), the Netherlands' LQTS Registry (n=93), and the Japanese LQTS Registry (n=82). All subjects or their guardians provided informed consent for the genetic and clinical studies.

### Phenotype Characterization

Routine clinical and ECG parameters were acquired at the time of enrollment in each of the registries. Follow-up was censored at age 41 years to avoid the influence of coronary disease on cardiac events. Measured parameters on the first recorded ECG included QT and R-R intervals in milliseconds, with QT corrected for heart rate by Bazett's formula. The QTc interval was expressed in its continuous form and categorized into 3 levels:  $<500$ , 500 to 530, and  $>530$  ms. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, therapy, and end points during long-term follow-up. LQTS-related cardiac events included syncope, aborted cardiac arrest, or unexpected sudden death without a known cause. Data common to all 3 LQTS registries involving genetically identified patients with type-1 genotype were electronically merged into a common database for the present study.

### Genotype Characterization

The KCNQ1 mutations were identified with the use of standard genetic tests performed in academic molecular-genetic laboratories including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, Tex; Mayo Clinic College of Medicine, Rochester, Minn; Boston Children's Hospital, Boston, Mass; Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; and Department of Clinical Genetics, Academic Medical Center, Amsterdam, Netherlands.

Genetic alterations of the amino acid sequence were characterized by location and by the specific mutation (missense, splice site, in-frame insertions/deletions, nonsense, stop codon, and frameshift). The transmembrane region of the KCNQ1-encoded channel was defined as the coding sequence involving amino acid residues from 120 through 355 (S5-pore-S6 region 285 to 355), with the N-terminus region defined before residue 120 and the C-terminus region after residue 355. Nineteen study patients had intron mutations predicted to disrupt the canonical splice-site domains. Fifty-one

subjects died of sudden cardiac death at a young age but did not have genotype studies. These 51 subjects were assumed to have the same KCNQ1 mutation as other affected members of their respective family. Twelve subjects had 2 mutations, one in the KCNQ1 gene and a second mutation in another LQTS ion channel gene; these 12 subjects are described separately and are not included in any of the tables or outcome analyses. Subjects with Jervell and Lange-Nielsen syndrome with deafness and 2 KCNQ1 mutations as well as those with 1 known KCNQ1 mutation and congenital deafness are not included in the present study.

The biophysical function of the mutant channels was classified as having dominant-negative effect ( $>50\%$  reduction in function) or haploinsufficiency ( $\leq 50\%$  reduction in function) on the basis of the following: (1) cellular expression studies for those with missense (n=21) and nonsense (n=2) mutations reported in the literature, with the functional information derived exclusively from heterologous expression studies; and (2) assumed loss of function for identified nonsense, splice site, in-frame deletion, and frameshift mutations (n=10) that have not yet been functionally characterized. Forty-one missense mutations and the 3 intron mutations that have not been functionally reported in cellular expression studies were categorized as unknown in terms of type of functional perturbation.

### Statistical Analysis

Differences in the univariate characteristics by specific groupings were evaluated by standard statistical methods. The primary end point was time to syncope, aborted cardiac arrest, or sudden death, whichever occurred first. The cumulative probability of a first cardiac event was assessed by the Kaplan-Meier method with significance testing by the log-rank statistic. The Cox proportional hazards survivorship model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of time-dependent cardiac events from birth through age 40 years.<sup>9</sup> Stratified and unstratified Cox regression models, allowing for time-dependent covariates, were fit to estimate the adjusted hazard ratio of each factor as a predictor of first cardiac events. We observed that sex was not proportional as a function of age with crossover in risk at age 13 years on univariate Kaplan-Meier analysis. To relax the assumption of proportional hazards for sex over the entire age range, separate nonparametric baseline hazard functions were allowed for male and female subjects via the stratified Cox model; then, to summarize the sex effect, sex was modeled in an unstratified Cox model as a time-dependent covariate (via an interaction with time), allowing for different hazard ratios by sex before and after age 13 years.

Because almost all the subjects were first- and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership.<sup>10</sup> All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported.

Patients who died suddenly at a young age from suspected LQTS and who did not have an ECG for QTc measurement were identified in the Cox models as "QTc missing." Prespecified covariate interactions were evaluated. The influence of time-dependent  $\beta$ -blocker therapy (the age at which  $\beta$ -blocker therapy was initiated) on outcome was determined by adding this variable to the final Cox model containing the various covariates.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Total Study Population

The spectrum and number of KCNQ1 mutations by location, type of mutation, and functional effect are presented in Table 1, with the location frequency of the mutations presented diagrammatically in Figure 1. A total of 77 different KCNQ1

TABLE 1. KCNQ1 Mutations by Location and Coding, Type of Mutation, and Functional Effect

Location and Coding*	No. of Subjects†	Type of Mutation	Functional Effect‡
N-terminus			
M1V	1	Missense	Unknown
G57V	1	Missense	Unknown
Transmembrane			
W120C	2	Missense	Unknown
T144A	7	Missense	Unknown
A150fs/133 [del CT 451-452]	2	Frameshift	Haploinsufficiency
E160K	3	Missense	Unknown
G168R	44	Missense	Unknown
Y171X [513 C>G]	6	Nonsense	Haploinsufficiency
R174H	2	Missense	Unknown
A178P	5	Missense	Dominant-negative effect (a)
Y184S	18	Missense	Unknown
G185S	10	Missense	Unknown
G189E	2	Missense	Unknown
G189R	4	Missense	Dominant-negative effect (b)
R190Q	4	Missense	Haploinsufficiency (b, c)
L191fs/90 [del TGC GC 572-576]	8	Frameshift	Haploinsufficiency
R195fs/40 [del G 585]	2	Frameshift	Haploinsufficiency
S225L	13	Missense	Dominant-negative effect (d)
A226V	3	Missense	Unknown
R237P	1	Missense	Unknown
D242N	3	Missense	Unknown
R243C	13	Missense	Haploinsufficiency (e)
V254 mol/L	59	Missense	Dominant-negative effect (b, f)
R258C	1	Missense	Haploinsufficiency
R259C	1	Missense	Haploinsufficiency (g)
L266P	15	Missense	Unknown
G269D	35	Missense	Dominant-negative effect (h)
G269S	25	Missense	Haploinsufficiency (i)
L273F	6	Missense	Dominant-negative effect (a)
I274V	1	Missense	Unknown
S277L	3	Missense	Unknown
Y278H	2	Missense	Unknown
E284K	2	Missense	Unknown
G292D	3	Missense	Unknown
F296S	2	Missense	Unknown
G306R	2	Missense	Dominant-negative effect (b, j)
V310I	1	Missense	Unknown
T312I	14	Missense	Dominant-negative effect (a)
G314S	8	Missense	Dominant-negative effect (h, k, l, m)
Y315C	10	Missense	Dominant-negative effect (d, n)
Y315S	1	Missense	Dominant-negative effect (h, m)
D317G	3	Missense	Unknown
P320H	1	Missense	Unknown
T322 mol/L	2	Missense	Unknown
G325R	3	Missense	Unknown
delF340 [del CTT 1017-1019]	7	In-frame deletion	Haploinsufficiency
A341E	9	Missense	Dominant-negative effect (b)
A341V	20	Missense	Dominant-negative effect (o)

TABLE 1. Continued

Location and Coding*	No. of Subjects†	Type of Mutation	Functional Effect‡
P343S	1	Missense	Dominant-negative effect (p)
A344A/sp [1032 G>A]	27	Splice site	Haploinsufficiency
A344V	17	Missense	Unknown
S349W	15	Missense	Unknown
L353P	4	Missense	Unknown
C-terminus			
Q357H	3	Missense	Unknown
R360G	3	Missense	Unknown
S373P	7	Missense	Unknown
K393N	10	Missense	Unknown
R397W	5	Missense	Unknown
P400fs/62 [ins C 1201-1022]	6	Frameshift	Haploinsufficiency
P448fs/13 [ins G 1344-1345]	11	Frameshift	Haploinsufficiency
I517T	3	Missense	Unknown
R518X [1552 C>T]	11	Nonsense	Haploinsufficiency (q)
M520R	3	Missense	Unknown
V524G	4	Missense	Unknown
Q530X [1588 C>T]	13	Nonsense	Haploinsufficiency (q)
R562 mol/L	2	Missense	Unknown
S566F	3	Missense	Unknown
I567S	6	Missense	Unknown
S571fs/20 [del C 1714]	3	Frameshift	Haploinsufficiency
R591C	5	Missense	Unknown
R591H	6	Missense	Haploinsufficiency (r)
R594Q	11	Missense	Haploinsufficiency (q)
D611Y	10	Missense	Haploinsufficiency (s)
A636fs/28 [del C 1909]	2	Frameshift	Haploinsufficiency
Intron			
IVS2+1 G>A	2	Splice site	Unknown
IVS4+5 G>A	2	Splice site	Unknown
IVS7+5 G>A	15	Splice site	Unknown

\*The numbers and letters refer to the amino acid coding of the mutant channel protein. The brackets contain the nucleotide code for deletions, frameshift, splice site, and nonsense mutations.

†Included in this table are 52 subjects who died suddenly at a young age. These subjects were from families with a known KCNQ1 mutation and were assumed to have their respective family mutation.

‡Dominant-negative effect is associated with >50% reduction whereas haploinsufficiency is associated with <50% reduction in ion channel repolarizing current. See text for details. Letters in parentheses refer to references that are available in the online-only Data Supplement.

mutations were identified. A majority of the mutations were localized to the S1 to S6 transmembrane domains (66%), and missense (single amino acid substitutions) accounted for 81% of all the mutations.

The phenotypic characteristics of patients enrolled in each of the 3 registries and by location and type of mutation are presented in Table 2. The clinical characteristics of the patients were similar among the 3 registries except for QTc duration and frequency of  $\beta$ -blocker use. The QTc interval was longer and cardiac events and  $\beta$ -blocker use were more frequent in patients with mutations in the transmembrane than in the C-terminus location.  $\beta$ -Blockers were used less frequently in patients from the Japanese registry than in patients from the other 2 registries. The frequency of first cardiac

events was higher in those with than without missense mutations. The clinical characteristics of the 19 subjects possessing intron mutations resembled those with transmembrane and missense mutations.

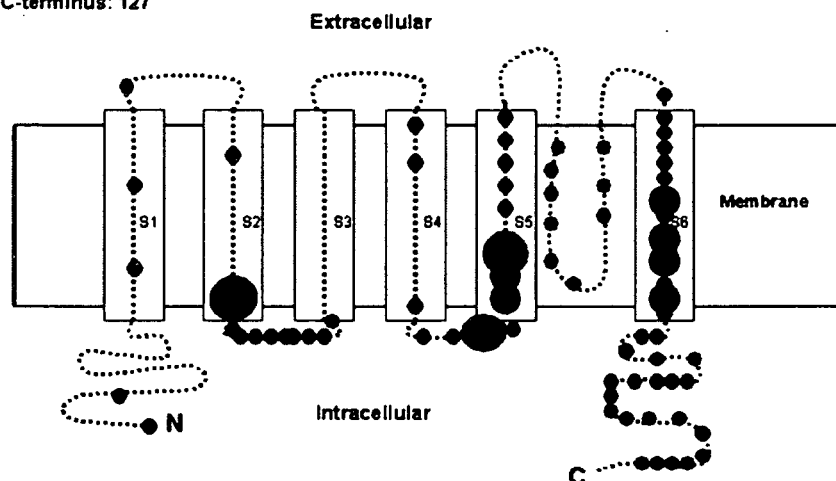
The QTc interval was significantly longer in the 12 patients with 2 mutations than in those with only single KCNQ1 mutations ( $570\pm 70$  versus  $480\pm 60$  ms;  $P<0.01$ ). All 12 patients with 2 mutations experienced at least 1 cardiac event.

The cumulative probabilities of first cardiac event by location and type of mutation are presented in Figure 2A and 2B, respectively. Significantly higher event rates were found in subjects with transmembrane than C-terminus mutations and in those with than without missense mutations, with the most rapid increase in event rates occurring during ages 7 to

# Subjects

N-terminus: 2  
 Transmembrane: 452  
 C-terminus: 127

Mutations in the KCNQ1 Channel



**Figure 1.** Frequency and location of 74 different mutations in the KCNQ1 potassium channel involving 581 subjects. The 19 subjects with 3 intron mutations are not included in this diagram. The  $\alpha$  sub-unit involves the N-terminus (N), 6 membrane-spanning segments, and the C-terminus portion (C). The size of the circles reflect the number of subjects with mutations at the respective locations, with the small circles indicating <15, medium-sized circles 15 to 30, and large circles >30 subjects.

20 years. In patients with transmembrane-localized mutations, the event rates for patients with mutations localized to the pore region (S5-pore-S6) were nearly identical to those with nonpore mutations (data not shown).

The findings from the Cox regression analysis for location and type of mutation are presented in Table 3. The clinical risk factors associated with first cardiac events involved males before age 13 years, females after age 13

**TABLE 2. Phenotypic Characteristics by Source of Subjects, Location of Mutation, and Type of Mutation**

Characteristics	Source of Subjects			Location of Mutation		Missense Mutation		Intron Mutation (n=19)
	United States (n=425)	Netherlands (n=93)	Japan (n=82)	Trans Membrane (n=452)	C-Terminus (n=127)	Yes (n=483)	No (n=98)	
Female, %	57	53	54	57	51	54	62	63
ECG at enrollment								
QTc†‡, ms	488±58	450±45	472±46	485±53	460±61	481±59	471±38	478±60
Therapy, %								
β-Blockers†‡	45	34	26	45	28	42	38	37
Pacemaker	2.4	0	0	1.5	2.4	1.4	3.1	0
Sympathectomy	0.5	0	0	0.4	0	0.4	0	0
Defibrillator	6.4	3.2	0	5.8	3.1	5.2	5.1	0
First cardiac event*†§, %	41	37	38	45	21	43	26	42
Syncope‡ (n=200)	35	31	29	38	17	36	21	32
Aborted cardiac arrest (n=15)	1.9	1.1	7.3	2.9	0.8	2.5	2.0	5.3
Death (n=23)	4.0	5.5	1.2	4.0	3.1	4.2	2.0	5.3
Ever cardiac event, %								
Syncope‡§	35	31	31	39	17	37	21	33
Aborted cardiac arrest†	2.4	15	8.8	5.3	3.2	5.4	2.0	11
Death	11	14	2.4	10	6.3	11	4.1	26

Plus-minus values are mean±SD. Percentages >10 are rounded to a whole number. The 600 subjects in this table include 51 subjects who died suddenly at a young age, were from families with known KCNQ1 mutation, and were assumed to have the family mutation. Patients with intron mutations are categorized separately and are not included in the location or missense categories. Seven subjects with transmembrane mutations and 1 with C-terminus mutations had missing data about the date of the first cardiac event. Eight subjects with missense mutations had missing data about the date of the first cardiac event. Numbers in parentheses indicate the total number of specific first cardiac events from the 3 sources of patients.

\*First cardiac event was syncope, aborted cardiac arrest, or sudden death, whichever occurred first.

†P<0.01 for the comparison of characteristics among the 3 sources of subjects.

‡P<0.01 for the comparison of characteristics between the 2 locations of the mutations.

§P<0.01 for the comparison of characteristics between missense yes and no.

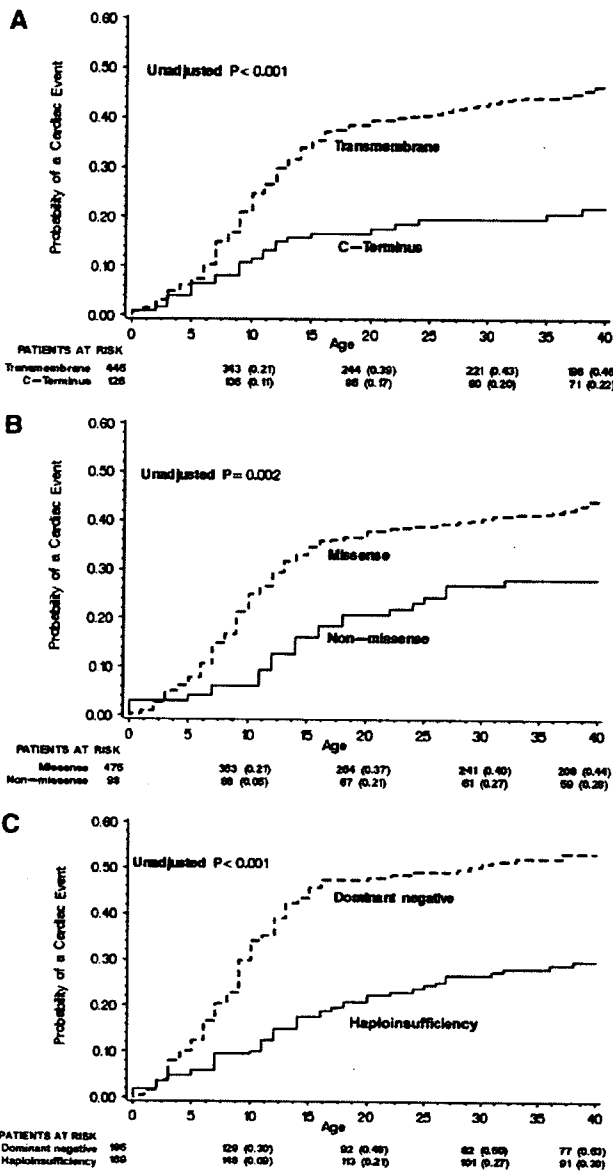


Figure 2. Kaplan-Meier estimate of the cumulative probability of a first cardiac event by location (A), type (B), and biophysical function of the mutation (C).

years, and longer QTc intervals. Mutations located in the transmembrane region of the channel made significant and independent contributions to the risk model, but missense mutations were not an independent risk factor. Three different intron mutations were present in 19 subjects from 4 families, and these intron mutations made a meaningful but nonsignificant contribution to the risk model. Prespecified interactions were investigated for their effect on cardiac events, and no significant interactions were found for transmembrane location by type of mutation, transmembrane location by QTc, or mutation type by QTc. Time-dependent  $\beta$ -blocker use was associated with a significant 74% reduction in the risk of first cardiac events ( $P < 0.001$ ).

TABLE 3. Cox Regression With Multiple Predictor Variables Including Location and Type of Mutations for First Cardiac Event

Variable	Hazard Ratio	95% CI	P
Netherlands:United States	1.15	0.74–1.78	0.55
Japan:United States	1.45	0.98–2.16	0.07
Male <13 y:female <13 y	1.72	1.25–2.38	<0.001
Female 13–40 y:male 13–40 y	2.27	1.30–3.96	<0.01
QTc 500–530 ms:QTc <500 ms	2.04	1.41–2.96	<0.001
QTc >530 ms:QTc <500 ms	3.25	2.25–4.69	<0.001
QTc missing*:QTc <500 ms	2.26	1.57–3.25	<0.001
Transmembrane:C-terminus	2.06	1.36–3.12	<0.001
Missense yes:no	1.33	0.86–2.05	0.20
Intron:C-terminus	2.45	0.98–6.11	0.06
Time-dependent $\beta$ -blocker use	0.26	0.14–0.49	<0.001

The Cox analysis involved 592 subjects with 445 transmembrane, 126 C-terminus, 2 N-terminus, and 19 intron mutations; 8 subjects were not included in this Cox analysis because of missing data about the date of their first cardiac event.

\*QTc missing category involves 47 subjects who died suddenly at a young age without a prior ECG.

### Biophysical Function and Outcome

The clinical implications of disordered biophysical function of the mutant KCNQ1 channels were investigated in a subset of 356 subjects with known or suspected alteration in ion channel function (see Methods for functional categorization). The clinical characteristics of patients with dominant-negative and haploinsufficiency ion channel dysfunction are presented in Table 4. Patients with mutations having dominant-negative ion current effects had a longer QTc interval and a higher frequency of cardiac events than subjects with mutations resulting in haploinsufficiency. The cumulative probabilities of a first cardiac event by the biophysical function of the mutations are presented in Figure 2C. As shown in Table 5, patients with mutations having

TABLE 4. Phenotypic Characteristics by Biophysical Function of the KCNQ1 Mutations in 356 Subjects

Characteristics	Dominant-Negative Effect (n=187)	Haploinsufficiency (n=169)
Female, %	51	61
ECG at enrollment		
QTc, * ms	500±60	470±50
Therapy, %		
$\beta$ -Blockers	47	37
Pacemaker	1.1	4.1
Sympathectomy	0.5	0
Defibrillator	4.8	7.7
First cardiac event*, %	53	27
Syncope	45	22
Aborted cardiac arrest	2.1	3.0
Death	5.3	2.4

Percentages >10 are rounded to a whole number. Two subjects had missing data about the date of their first cardiac event.

\* $P < 0.01$ .

**TABLE 5. Cox Regression With Multiple Predictor Variables Including Ion Channel Dysfunction for First Cardiac Events**

Variable	Hazard Ratio	95% CI	P
Netherlands:United States	2.78	1.48-5.23	<0.01
Japan:United States	1.63	1.02-2.63	0.04
Male <13 y:female <13 y	1.94	1.29-2.91	<0.01
Female 13-40 y:male 13-40 y	1.95	0.99-3.87	0.06
QTc 500–530 ms:QTc <500 ms	1.88	1.18-2.99	<0.01
QTc >530 ms:QTc <500 ms	3.22	2.06-5.05	<0.001
QTc missing*:QTc <500 ms	2.07	1.29-3.33	<0.01
Dominant-negative:haploinsufficiency	2.26	1.56-3.25	<0.001
Time-dependent $\beta$ -blocker use	0.21	0.09-0.48	<0.001

The analysis involved 354 subjects with known or suspected ion channel dysfunction; 2 subjects were not included because of missing data about the date of their first cardiac event.

\*The QTc missing category involves 26 patients who died suddenly at a young age without a prior ECG.

dominant-negative functional effects experienced a significantly greater risk for cardiac events than those with haploinsufficiency (hazard ratio, 2.26; 95% CI, 1.56 to 3.25;  $P < 0.001$ ) after adjustment for relevant covariates including QTc and gender effects by age group.  $\beta$ -Blocker use was associated with a significant 79% reduction in first cardiac events in this subset of patients. Because substantial colinearity exists for transmembrane mutations, missense mutations, and mutations with dominant-negative biophysical function, the individual effects of these 3 mutation parameters could not be ascertained reliably in the same Cox model.

### Discussion

The main results of the present study from 600 patients having a spectrum of KCNQ1 mutations derived from 3 LQTS registries are significantly higher cardiac event rates in patients with transmembrane mutations and in patients with mutations having a putative dominant-negative effect on the repolarizing  $I_{Ks}$  current. The effect of these genetically determined factors is independent of traditional clinical risk factors and of  $\beta$ -blocker therapy.

Since 1995, when the first 2 genes responsible for LQTS were identified,<sup>11,12</sup> molecular genetic studies have revealed a total of 9 forms of congenital LQTS caused by mutations in genes involving potassium channel (LQT-1, -2, -5, -6, and -7), sodium channel (LQT-3, -9), and calcium channel proteins (LQT-8) as well as a membrane-adapter protein (LQT-4).<sup>2,13</sup> Genotype–phenotype studies have enabled us to stratify risk and to treat more specifically patients with LQT-1, LQT-2, and LQT-3 subtypes of this genetic disorder. LQT-1, the most common form of LQTS, accounts for  $\approx 50\%$  of genotyped patients<sup>4,14</sup> and has more variable expressivity and incomplete penetrance than the other forms.<sup>15</sup> Mutation location and knowledge of the functional effects of the mutation provide additional risk information beyond the clinical risk factors and the genotype, at least for LQT-1, and this information should contribute to improved risk stratification and more focused management of these higher-risk patients.

Mutations in KCNQ1 are responsible for defects in the slowly activating component of the delayed rectifier current  $I_{Ks}$ .<sup>16</sup> This current is the main repolarizing current at increased heart rate and is highly sensitive to catecholamines.<sup>3</sup> We speculate that  $I_{Ks}$  channels with transmembrane mutations might have reduced responsiveness to the regulatory  $\beta$ -adrenergic signaling of the ion-conduction pathway with more impairment of shortening of the QTc with exercise-related tachycardia than mutations in the C-terminus region.

Functional  $I_{Ks}$  channels result from the coassembly of 4 KCNQ1-encoded subunits. A mutated gene encodes a protein with aberrant function, and the presence of both normal and abnormal proteins in the ion channel contributes to a  $>50\%$  reduction in ion channel function (dominant-negative effect). An alternative mechanism of reduced repolarizing KCNQ1  $K^+$  current is the inability of mutated subunits to coassemble with normal gene products, such as occurs with a trafficking defect, resulting in a  $\leq 50\%$  reduction in channel function (haploinsufficiency). With only 1 exception,<sup>17</sup> this is the case for all studied truncating mutations leading to incomplete proteins. Our assumption that truncated proteins (based on frameshift nonsense mutations) lead to haploinsufficiency seems justified. The biophysical effect of missense mutations is unpredictable, and both haploinsufficiency and dominant-negative effects have been described. In the absence of reported biophysical studies, missense mutations were classified as unknown.

Previous attempts to identify a genotype–phenotype relationship for KCNQ1 mutations failed to reach consensus on the clinical outcome of the type and site of mutations.<sup>7,8</sup> Relatively small numbers and different ethnic background of the previously reported patients with the LQT-1 genotype might be responsible for the discrepant results. The present larger study allows us to demonstrate for the first time that the biophysical effect clearly affects the clinical outcome (ie, dominant-negative mutations are associated with a more severe phenotype than are mutations conferring haploinsufficiency [Figure 2C], even after adjustment for relevant covariates [Table 5]). The risk observed in 19 subjects with 3 different intron mutations was not quite significant ( $P = 0.06$ ), possibly because of small numbers, but the magnitude of the risk effect was similar to the risk accompanying transmembrane mutations. Although these intron mutations produced splice-site alterations predicted to affect the transmembrane portion of the ion channel, we used a separate categorization of intron mutations in view of the limited understanding of the structural alterations and functional effects resulting from these exon-skipping intron mutations.

A few additional findings from this large genotype–phenotype study of type-1 LQTS patients emphasize high risk for first cardiac events during adolescence, a crossover in risk by sex at approximately age 13 years, and a lower rate of first cardiac events in the adult years than in the younger years. These findings are not especially new,<sup>18,19</sup> but the present study highlights their presence in type-1 LQTS.

### Study Limitations

The present study used the biophysical function of mutations reported in the literature in only a portion of the mutations



that were included (see references associated with Table 1 in the online-only Data Supplement). The published studies were from many different laboratories with the use of different cellular heterologous expression systems involving *Xenopus* oocytes and other cells at both room and physiological temperatures. Although such nonuniform testing may have contributed to some inconsistency in the categorized biophysical function, the finding of a significantly higher event rate in mutations with dominant-negative than with haploinsufficient effects (hazard ratio, 2.26;  $P < 0.001$ ) is unlikely to have resulted from the nonuniform testing. Unfortunately, we did not have the resources to perform such uniform testing in all 77 mutations presented in the present study.

Once a mutation was identified in KCNQ1, thorough genetic sequencing was not performed routinely in all the ion channel genes to look for second mutations. Thus, some of the patients included in the analysis may have had a second mutation in addition to the identified KCNQ1 mutation. It is estimated that  $\approx 10\%$  of genotype LQTS patients may carry a second mutation, and those with  $>1$  mutation could contribute to some of the findings in our study. In addition, it is possible that some of the reported mutations (Table 1) are simply uncommon sequence mutations, but this is relatively unlikely because all the subjects in the present study were derived from families in which the proband had QTc prolongation not due to a known cause.

The outcome analyses included subjects from families with a known KCNQ1 mutation who died suddenly and unexpectedly at a young age and were classified as LQTS-related death with the same mutation that was present in the family. It is possible that a few of these subjects could have died from a non-LQTS cause or had an LQTS mutation different from the family mutation, but we think the error rate is likely to be small. The number of deaths and aborted cardiac arrest events is small, and there is insufficient power to evaluate the risk association of the genotype characteristics with these endpoint events in a multivariate time-dependent model.

### Conclusions

The present study confirms that in patients with type-1 LQTS, longer QTc intervals are associated with higher cardiac event rates and that male patients are generally younger than female patients at first cardiac events.<sup>20,21</sup> The new findings from the present study are that transmembrane mutations and mutations with dominant-negative functional effect adversely influence the outcome of this disorder independent of traditional clinical risk factors and  $\beta$ -blocker therapy. The present study was not designed to assess the effectiveness of different therapies in patients with KCNQ1 mutations. The findings presented do not provide justification for using specific genotype characteristics to identify patients for implanted defibrillator therapy.

### Note Added in Proof

After this article was accepted for publication, we noted the recent article by Tsuji et al, in which the A344A/sp [1032G>A] mutation that we categorized as haploinsufficient (Table 1) was reported to have a weak dominant-

negative effect.<sup>22</sup> We reran the KCNQ1 data recategorizing the 27 A344A/sp [1032 G>A] mutations as dominant-negative. Negligible changes occurred in the results as presented in Table 5 and Figure 2C; the hazard ratio for dominant-negative:haploinsufficiency (Table 5) was unchanged at 2.26 ( $P < 0.001$ ).

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### Disclosures

Dr Ackerman is a consultant for Clinical Data (formerly Genaisance Pharmaceuticals) with respect to the FAMILION genetic test for cardiac ion channel mutations. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

Type-1 long-QT syndrome is caused by loss-of-function mutations in the KCNQ1-encoded  $I_{Ks}$  cardiac potassium channel. In the present study involving 600 patients having a spectrum of KCNQ1 mutations derived from 3 long-QT syndrome registries, we found that cardiac event rates are increased significantly in patients with mutations located in the transmembrane region of the potassium channel and in patients with mutations having a putative dominant-negative effect on the repolarizing  $I_{Ks}$  current. The effects of these genetically determined factors are independent of traditional clinical risk factors and of  $\beta$ -blocker therapy. Mutation location and knowledge of functional effects of the mutation provide additional risk information beyond the clinical risk factors and the genotype, at least for type-1 long-QT syndrome, and this information should contribute to improved risk stratification and more focused management of these higher-risk patients.

# Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation

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**BACKGROUND** Some patients with Brugada syndrome experience an electrical storm of ventricular fibrillation (VF).

**OBJECTIVE** The purpose of this study was to investigate the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics, acute and subsequent chronic treatment, and follow-up data of patients with Brugada syndrome associated with electrical storm of VF.

**METHODS** Sixty-seven patients with Brugada syndrome (65 men and 2 women, age  $46 \pm 14$  years) were divided into three groups: 7 patients with a history of electrical storm of VF (group I), 39 symptomatic patients with documented VF and/or syncope (group II), and 21 asymptomatic patients (group III). Electrical storm was defined as three or more episodes of VF per day recorded by the memory of an implantable cardioverter-defibrillator.

**RESULTS** No significant differences were observed among the three groups with regard to clinical (age at diagnosis, familial history of sudden cardiac death), laboratory (SCN5A mutation and serum potassium level), electrocardiographic and electrophysi-

ologic characteristics, and follow-up duration after diagnosis. However, arrhythmic events during follow-up after diagnosis and number of arrhythmic events per patient were significantly higher in group I compared with groups II and III. Isoproterenol infusion ( $0.003 \pm 0.003 \mu\text{g}/\text{kg}/\text{min}$  for  $24 \pm 13$  days) completely suppressed electrical storm of VF in all five patients treated and was successfully replaced with oral medications, including denopamine, quinidine, isoproterenol, cilostazol, and bepridil alone or in combination.

**CONCLUSION** No specifically clinical, laboratory, electrocardiographic, and electrophysiologic characteristics were recognized in patients with Brugada syndrome associated with electrical storm of VF. Isoproterenol infusion was effective as an acute treatment in suppressing electrical storm of VF and was successfully replaced with chronic oral medications.

**KEYWORDS** Brugada syndrome; Ventricular fibrillation; Electrical storm; Sudden cardiac death; Isoproterenol; Quinidine (Heart Rhythm 2007;4:695-700) © 2007 Heart Rhythm Society. All rights reserved.

## Introduction

In 1992, Brugada and Brugada<sup>1</sup> described eight patients with a history of aborted sudden cardiac death (SCD) due to ventricular fibrillation (VF) and a distinct ECG pattern consisting of right bundle branch block and ST-segment elevation in the right precordial leads ( $V_1$ - $V_3$ ) in the absence of any structural heart diseases.<sup>1-7</sup> At present, there is no specific pharmacologic treatment to prevent sudden death in patients with Brugada syndrome. Some patients with Bru-

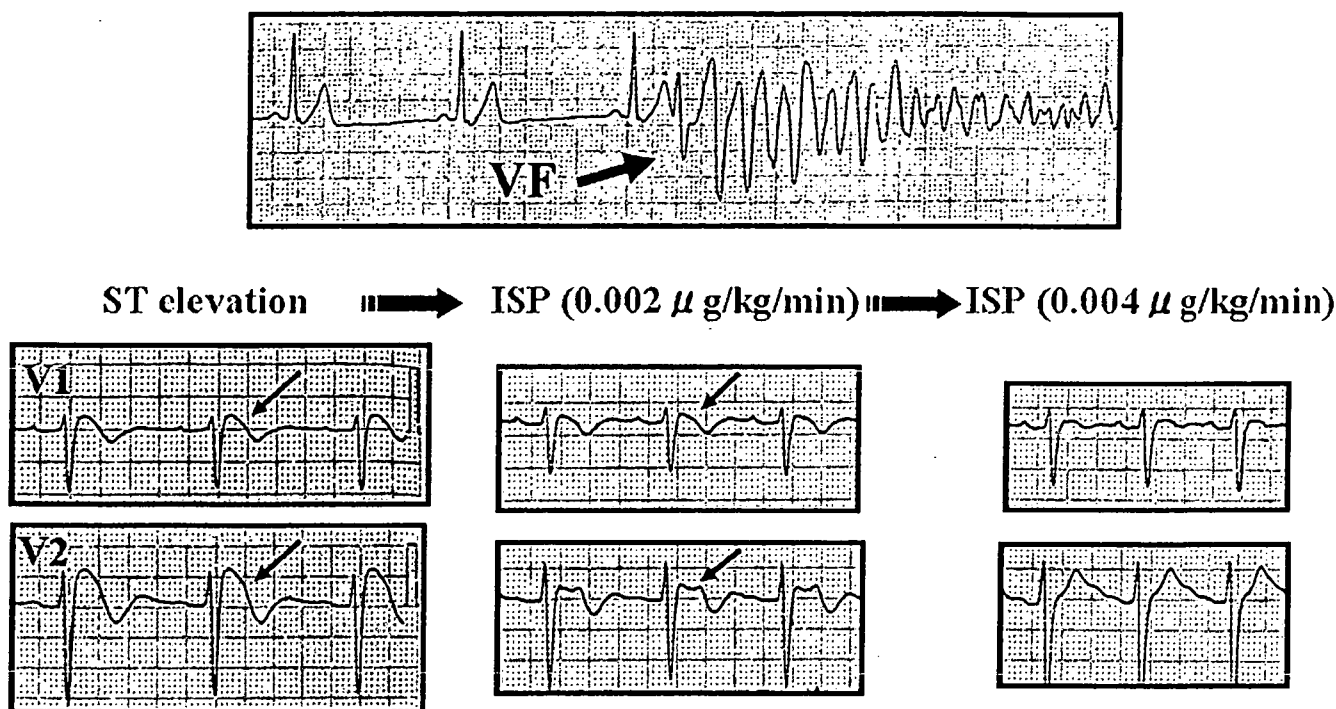
gada syndrome experience an electrical storm of VF. Isoproterenol, a  $\beta$ -adrenergic agonist, is reported to decrease ST elevation and suppress repetitive episodes of VF in patients with Brugada syndrome probably because of its effect to augment L-type calcium current ( $I_{Ca-L}$ ).<sup>8-12</sup> However, clinical characteristics and subsequent chronic management following acute therapy with isoproterenol infusion in patients with Brugada syndrome associated with electrical storm of VF is still unclear. In the present study, we investigated the clinical, electrocardiographic, and electrophysiologic characteristics and acute and subsequent chronic treatment in patients with Brugada syndrome associated with electrical storm of VF.

## Methods

### Study population

The study population consisted of 67 consecutive patients (65 men and 2 women, age 19-67 years, mean  $46 \pm 14$  years) with Brugada syndrome who were admitted to the

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**Figure 1** Effects of isoproterenol (ISP) infusion on ST-segment elevation and ventricular fibrillation (VF) in a patient with electrical storm of VF. Isoproterenol (0.002  $\mu\text{g}/\text{kg}/\text{min}$ ) decreased J-point amplitude and changed coved-type to saddleback-type ST-segment elevation in lead V<sub>2</sub>. Increasing dose of isoproterenol (0.004  $\mu\text{g}/\text{kg}/\text{min}$ ) normalized ST-segment elevation in lead V<sub>2</sub> and completely suppressed repetitive episodes of VF.

National Cardiovascular Center, Osaka, Japan, between 1994 and 2004. Brugada syndrome was diagnosed when type 1 coved-type ST-segment elevation ( $\geq 0.2$  mV at J point) was observed in more than one of the right precordial leads (V<sub>1</sub>–V<sub>3</sub>) in the presence or absence of a sodium channel blocker and in conjunction with one of the following: documented VF, polymorphic ventricular tachycardia (VT), family history of SCD at age younger than 45 years, coved-type electrocardiogram (ECG) in family members, inducibility of VF with programmed electrical stimulation, syncope, or nocturnal agonal respiration.<sup>13</sup> Physical examination showed no abnormal findings, and no evidence of structural heart diseases was demonstrated by echocardiogram in any patients. Informed consent was obtained from all patients. The 67 patients with Brugada syndrome were divided into three groups; 7 patients (6 men) with a history of electrical storm of VF (group I), 39 symptomatic patients (38 men) with documented VF and/or syncope (group II), and 21 asymptomatic patients (21 men, group III).

The 21 patients in group III were diagnosed as having Brugada syndrome according to the following combination of diagnostic criteria in addition to the type 1 Brugada ECG: 11 patients with VF induction during electrophysiologic study, 4 patients with a family history of SCD, 2 patients with documented nonsustained polymorphic VT, 2 patients with nocturnal agonal respiration, and 2 patients with augmentation of ST elevation at early recovery phase after exercise. Electrical storm was defined as three or more episodes of VF per day recorded by

the memory of an implantable cardioverter-defibrillator (ICD) for at least 1 day. We retrospectively compared clinical, laboratory, electrocardiographic and electrophysiologic characteristics and follow-up data among the three groups. In the present study, patients were entered into the study upon diagnosis of Brugada syndrome. Study procedures, including 12-lead ECG, signal-averaged ECG, and electrophysiologic study, were performed during first symptomatic in-hospital admission (groups I and II) or in-hospital admission for evaluation of Brugada ECG (group III).

#### Twelve-lead ECG

Twelve-lead ECG data were recorded at a paper speed of 25 mm/s during sinus rhythm in the supine resting state.

#### Signal-averaged ECG

The late potential was analyzed using a signal-averaged ECG system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI, USA). Three parameters were assessed using a computer algorithm: (1) total filtered QRS duration, (2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes ( $V_{40}$ ), and (3) duration of low-amplitude signals  $<40$   $\mu\text{V}$  of the filtered QRS complex ( $T_{40}$ ). A late potential was considered present when the two criteria ( $V_{40}$  38 ms) were fulfilled.

#### Electrophysiologic study

Electrophysiologic study was conducted without any antiarrhythmic drugs after informed consent was obtained. Pro-

**Table 1** Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics and follow-up

	Group I (n = 7)	Group II (n = 39)	Group III (n = 21)	P value
<b>Clinical characteristics</b>				
Age at diagnosis (years)	49.5 ± 15.9	45.5 ± 12.5	47.5 ± 11.4	NS
Previous VF or aborted cardiac arrest before diagnosis (%)	4/7 (57%)	24/39 (62%)	0/21 (0%)	<.05
Previous syncope alone before diagnosis (%)	3/7 (43%)	15/39 (38%)	0/21 (0%)	<.05
Family history of sudden cardiac death (%)	1/7 (14%)	3/39 (8%)	4/21 (19%)	NS
ICD placement (%)	7/7 (100%)	32/39 (82%)	12/21 (57%)	<.05
Duration after ICD placement (years)	8.2 ± 7.4	8.2 ± 2.3	5.3 ± 0.9	NS
<b>Laboratory characteristics</b>				
SCN5A mutation (%)	1/7 (14%)	3/39 (8%)	2/21 (10%)	NS
Serum potassium (mEq/L)	4.0 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	NS
<b>Electrocardiographic characteristics</b>				
Spontaneous coved-type ST elevation (%)	4/7 (57%)	12/39 (31%)	10/21 (48%)	NS
J-point amplitude (mV)	0.35 ± 0.1	0.29 ± 0.2	0.37 ± 0.2	NS
QRS duration (ms)	103 ± 15	106 ± 17	103 ± 20	NS
PQ interval (ms)	159 ± 45	176 ± 37	167 ± 18	NS
Late potential (%)	4/6 (67%)	22/36 (62%)	9/19 (47%)	NS
Augmentation of ST elevation at early recovery phase after exercise (%)	5/6 (83%)	15/31 (48%)	8/17 (47%)	NS
<b>Electrophysiologic characteristics</b>				
Induction of VF (%)	4/7 (57%)	21/30 (70%)	11/15 (65%)	NS
Mode				
Triple	2	9	7	
Double	2	10	4	
Single	0	0	0	
HV interval (ms)	45 ± 10	44 ± 13	46 ± 12	NS
<b>Follow-up</b>				
Follow-up duration after diagnosis (years)	9.5 ± 4.8	8.7 ± 4.5	5.4 ± 1.2	NS
Arrhythmic events during follow-up (%)	7/7 (100%)	11/39 (28%)	2/21 (9%)	<.05
No. of arrhythmic events per patient	14.7	1.1	0.1	<.01
Electrical storm during follow-up (%)	7/7 (100%)	0/39 (0%)	0/7 (0%)	<.01
Duration between diagnosis and first electrical storm (years)	4.6 ± 4.7	NA	NA	
Follow-up duration after electrical storm (years)	5.0 ± 1.5	NA	NA	
Arrhythmic events after electrical storm (%)	5/7 (71%)	NA	NA	

ICD = implantable cardioverter-defibrillator; VF = ventricular fibrillation.

grammed electrical stimulation was performed from the right ventricular apex and right ventricular outflow tract with up to triple extrastimuli. The last extrastimulus was given up to 180 ms in older cases and up to 200 ms in recent cases. Induction of VF requiring direct cardioversion and/or polymorphic VT lasting >30 seconds was considered positive.

### Acute treatment

If a patient had at least one episode of VF due to electrical storm of VF after admission, isoproterenol infusion was started until heart rate increased by 20% (Figure 1). If VF did not occur after admission, isoproterenol infusion was not used as an acute treatment, but oral medication (denopamine, an  $\alpha + \beta$ -adrenergic agonist, or quinidine) was prescribed.

### Chronic treatment

After repetitive episodes of VF were completely suppressed by isoproterenol infusion for more than 3 days, isoproterenol infusion was replaced with oral medications. Oral denopamine was prescribed initially. If VF recurred, other oral medications also were prescribed (quinidine, isoproterenol, cilostazol, bepridil).

### Follow-up

All patients were followed up at the outpatient clinic of the National Cardiovascular Center.

### Statistical analysis

Quantitative values are expressed as mean ± SD. Statistical significance of differences was analyzed by Chi-square test or one-way analysis of variance among the three groups (group I vs group II vs group III).  $P < .05$  was considered significant.

### Results

#### Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics of the three groups

The average number of VF episodes at electrical storm was  $9.1 \pm 6.8$  (3–20) in the 7 group I patients. No specific triggers (e.g., fever, stress, drugs or concomitant illness) for the electrical storm have been noted.

Comparison of the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics among the three groups is given in Table 1. There were no significant differences with regard to age at diagnosis, familial history

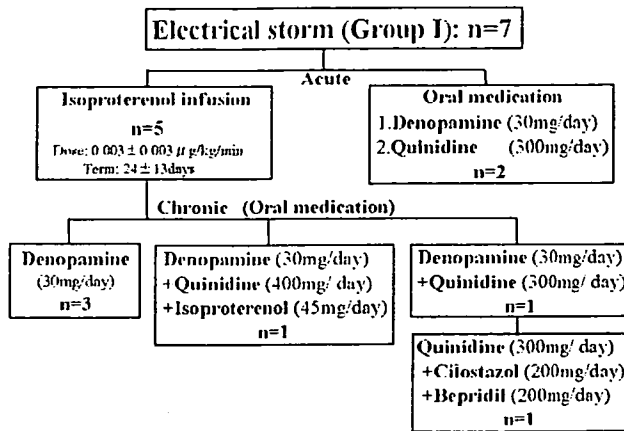


Figure 2 Summary of acute and subsequent chronic treatment in the seven patients associated with electrical storm of ventricular fibrillation.

of SCD, duration after ICD placement, *SCN5A* mutation, and serum potassium level among the three groups. There were no significant differences in previous VF or aborted cardiac arrest before diagnosis and previous syncope alone before diagnosis between groups I and II. Four patients had a history of VF or aborted cardiac arrest before diagnosis, and 3 patients in group I had previous syncope alone before diagnosis. An ICD was implanted before electrical storm of VF in all 7 patients.

No significant differences were observed among the three groups in the electrocardiographic characteristics at diagnosis with regard to J-point amplitude, QRS duration, PQ interval, and incidence of spontaneous coved-type ST elevation, late potentials, and augmentation of ST elevation at early recovery phase after exercise testing.

No significant differences in the frequency and mode of VF induction and HV interval during electrophysiologic study were observed among the three groups.

No significant differences were observed among the three groups during follow-up after diagnosis. However, arrhythmic events during follow-up after diagnosis and number of arrhythmic events/patients were significantly higher in group I vs groups II and III. Average duration between diagnosis and first electrical storm in group I was  $4.6 \pm 4.7$  years. Subsequent arrhythmic events after electrical storm were observed in 5 of the 7 group I patients.

#### Acute and chronic treatment for electrical storm of VF

At the electrical storm in the 7 group I patients, no intravenous antiarrhythmic agents (e.g., lidocaine or amiodarone) or sedation had been used before starting isoproterenol infusion. ST-segment elevation was augmented at the electrical storm compared with that at baseline ( $V_1$ :  $0.14 \pm 0.07$  vs  $0.09 \pm 0.04$  mV;  $V_2$ :  $0.38 \pm 0.09$  vs  $0.29 \pm 0.07$  mV). However, this difference did not reach statistical significance.

Figure 1 shows the acute effect of isoproterenol infusion on the electrical storm of VF in a representative patient with Brugada syndrome. Continuous infusion of isoproterenol

( $0.002 \mu\text{g/kg/min}$ ) decreased the J-point amplitude and changed coved-type to saddleback-type ST-segment elevation in lead  $V_2$ . Increasing dose of isoproterenol ( $0.004 \mu\text{g/kg/min}$ ) normalized ST-segment elevation in lead  $V_2$  and completely suppressed repetitive episodes of VF.

Figure 2 summarizes the acute and subsequent chronic treatment of the 7 patients with electrical storm of VF. Isoproterenol infusion was used as acute treatment in 5 of the 7 patients with electrical storm. Average dose of isoproterenol infusion was  $0.003 \pm 0.003 \mu\text{g/kg/min}$ . Average term of isoproterenol infusion ( $24 \pm 13$  days) was required because of difficulty in discontinuing or decreasing isoproterenol infusion because of VF recurrence. Isoproterenol completely suppressed electrical storm of VF in all 5 patients. The remaining 2 patients were prescribed oral medication (denopamine 30 mg/day and quinidine 300 mg/day, respectively) because no additional VF episodes occurred after admission.

Isoproterenol infusion was successfully replaced with oral medication in the first 5 patients: 3 with denopamine (30 mg/day), 1 with a combination of denopamine (30 mg/day), quinidine (400 mg/day), and isoproterenol (45 mg/day), and 1 with a combination of denopamine (30 mg/day) and quinidine (300 mg/day).

Average follow-up duration after electrical storm in the 7 group I patients was  $5.0 \pm 1.5$  years. In the 3 patients discharged with denopamine alone following isoproterenol infusion, two VF episodes were recorded in ICD memory for 68 months in 1 patient but no VF episodes in the remaining 2 patients (51 months and 77 months, respectively). Four VF episodes were recorded for 76 months in the patient who was discharged with a combination of denopamine, quinidine, and isoproterenol. The last patient, who was discharged with a combination of denopamine and quinidine, experienced another electrical storm of VF 6 months later after discontinuation of denopamine due to palpitation. Isoproterenol infusion was used again after readmission, and a combination of quinidine (300 mg/day), cilostazol (200 mg/day), and bepridil (200 mg/day) could successfully replace the isoproterenol infusion. VF did not recur for 18 months after readmission in this case. In the 2 patients in whom isoproterenol infusion was not used as an acute treatment, 1 patient who was discharged with denopamine experienced 6 VF episodes for 47 months, and the other patient who was discharged with quinidine had 7 VF episodes for 72 months.

#### Discussion

The major findings of this study were as follows: (1) no specifically clinical, laboratory, electrocardiographic, and electrophysiologic characteristics were recognized in patients with Brugada syndrome associated with electrical storm of VF, (2) continuous infusion of isoproterenol normalized ST-segment elevation and completely suppressed the electrical storm of VF as an acute treatment, and (3) oral medications including denopamine, quinidine, isoprote-

nol, cilostazol, and bepridil successfully replaced isoproterenol infusion as a chronic treatment.

### Characteristics of Brugada patients associated with electrical storm of VF

Identification of high-risk patients with Brugada syndrome associated with electrical storm of VF and elucidation of their clinical characteristics are important issues. Brugada syndrome usually manifests during adulthood, with a mean age at sudden death of  $41 \pm 15$  years.<sup>14</sup> It is reported that a family history of unexplained sudden death is present in approximately 20%–40% of Brugada Proband in Western countries and less (15–20%) in Japan, and that *SCN5A* mutations account for only 18%–30% of clinically diagnosed Brugada patients.<sup>8,14–16</sup> Low serum potassium level is suggested to be a predisposing factor for VF in patients with Brugada syndrome.<sup>14</sup> However, no significant differences in these clinical characteristics were observed between patients with and without a history of electrical storm of VF. Moreover, 12-lead electrocardiographic parameters and HV interval during electrophysiologic study were no different between patients with and those without an electrical storm of VF. Approximately 60%–70% of patients with Brugada syndrome show late potentials detected by signal-averaged ECG.<sup>14,17</sup> During treadmill exercise testing, augmentation of ST-segment elevation in the right precordial leads compared with that at baseline occasionally is recorded at early recovery phase after exercise (1 or 2 minutes) in Brugada patients. VF or sustained polymorphic VT is induced in approximately 50%–70% of Brugada patients during electrophysiologic study.<sup>8,15,16,18</sup> However, in the present study, frequency of late potentials and ST-segment augmentation after exercise, and inducibility of VF were no different between patients with and those without a history of electrical storm of VF. Although triggering or predisposing factors for electrical storm of VF and characteristics of Brugada patients associated with an electrical storm of VF remain unclear, in this study all 7 patients who experienced electrical storm of VF had arrhythmic events during follow-up after diagnosis. Therefore, our data provided further support for the requirement of ICD placement in Brugada patients with previous episodes of arrhythmic events.

### Acute management of Brugada patients associated with electrical storm of VF

Experimental studies have suggested that isoproterenol, a  $\beta$ -adrenergic agonist, decreases ST-segment elevation and suppresses VF by strongly augmenting  $I_{Ca-L}$  in an experimental model of Brugada syndrome.<sup>19,20</sup> Several clinical studies reported the protective effect of isoproterenol in normalizing ST-segment elevation and suppressing episodes of VF.<sup>8–12</sup> Watanabe et al<sup>21</sup> systematically reported that isoproterenol suppressed repetitive ventricular arrhythmia in patients with Brugada syndrome. In the present study, continuous infusion of isoproterenol attenuated ST-segment elevation and completely prevented repetitive ep-

isodes of VF in all 5 patients treated and therefore is considered to be first-line acute treatment of electrical storm of VF in Brugada syndrome.

### Adjunctive chronic oral treatment

Although isoproterenol infusion is effective in preventing repetitive episodes of VF at electrical storm, discontinuation or decrease of isoproterenol infusion often is difficult because of VF recurrence. In such cases, chronic oral medication usually is required to decrease and discontinue isoproterenol infusion. Several oral agents can be candidates as adjunctive chronic treatment to replace isoproterenol infusion and reduce the incidence of VF episodes subsequently in patients with Brugada syndrome associated with electrical storm of VF.

In the present study, several oral agents, including denopamine, quinidine, isoproterenol, cilostazol, and bepridil alone or in combination, were effective in replacing isoproterenol infusion. Especially, oral denopamine, an  $\alpha + \beta$ -adrenergic stimulant, was effective as a chronic treatment, probably by increasing  $I_{Ca-L}$ . Quinidine, a class IA sodium channel blocker, has a relatively strong effect in blocking  $I_{to}$  and has been proved effective in suppressing a spontaneous episode of VF in patients with Brugada syndrome.<sup>2–26</sup> Cilostazol, a phosphodiesterase III inhibitor that increases  $I_{Ca-L}$ , is reported to be effective in suppressing VF in Brugada syndrome.<sup>2–7</sup> More recently, bepridil is reported to suppress the incidence of VF episodes, probably by blocking  $I_{to}$ .<sup>2–8</sup> Although there was small number of Brugada patients associated with electrical storm of VF in whom adjunctive chronic effect of these agents could be examined, each agent alone or in combination was effective as an oral chronic treatment. Further systematic evaluation of the usefulness of these oral agents in larger numbers of Brugada patients is required to make a definitive conclusion.

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# Participation of a concealed atriohisian tract in the reentrant circuit of the slow-fast type of atrioventricular nodal reentrant tachycardia

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**BACKGROUND** The retrograde fast pathway in typical atrioventricular nodal reentrant tachycardia (AVNRT) exhibits marked variation in its electrophysiologic properties.

**OBJECTIVE** The purpose of this study was to characterize the retrograde fast pathway and localize the lower turnaround site of the reentrant circuit in typical AVNRT.

**METHODS** Seventy-four patients with typical AVNRT were divided into two groups according to the response of the retrograde fast pathway to intravenous administration of adenosine triphosphate (ATP) during ventricular pacing: ATP-S [ $n = 47$  (63.5%)] with and ATP-R without [ $n = 27$  (36.5%)] His-atrial (H-A) block. H-A intervals were measured from the most proximal His-bundle electrogram to the earliest atrial activation during the tachycardia (HAT) and entrainment pacing from the parahisian right ventricular region (HAe). It was postulated that the HAT was the difference in conduction time between the lower common pathway ( $x$ ) and retrograde fast pathway ( $y$ ) ( $HAT = y - x$ ), whereas HAe was

the sum of the two ( $HAe = y + x$ ). Hence,  $x = (HAe - HAT)/2$ .  $x > 0$  suggested the presence of a lower common pathway, whereas  $x < 0$  suggested the absence of a lower common pathway and lower turnaround site within the His bundle.

**RESULTS**  $x$  was significantly smaller in ATP-R than ATP-S ( $-6 \pm 5$  vs  $4 \pm 4$  ms,  $P < .05$ ) and was  $< 0$  in 23 (85%) of 27 ATP-R patients. The maximal increment in H-A interval during ventricular pacing was significantly longer in ATP-S than ATP-R ( $35 \pm 33$  vs  $2 \pm 2$  ms,  $P < .05$ ).

**CONCLUSION** A concealed atriohisian tract totally bypassing the atrioventricular node constituted the retrograde fast pathway in one third of all typical AVNRT cases.

**KEYWORDS** Concealed atriohisian tract; Lower common pathway; Adenosine triphosphate; Lower turnaround; Atrioventricular nodal reentrant tachycardia

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## Introduction

Typical (slow-fast form) atrioventricular nodal reentrant tachycardia (AVNRT) is amenable to radiofrequency catheter ablation targeting the slow pathway.<sup>1</sup> However, controversy has been ongoing for several decades as to whether AV nodal tissue, called the "lower common pathway," exists between the lower turnaround of the reentrant circuit and the His bundle.<sup>2-6</sup> Miller et al<sup>2</sup> reported that a lower common pathway was present in 75% of typical AVNRT, whereas Heidbuchel et al<sup>5,6</sup> postulated that the lower common pathway was absent in 94% of typical AVNRT, and that the lower turnaround site might be located within the proximal His bundle. The electrophysiologic properties of the retrograde fast path-

way in individual human hearts with typical AVNRT demonstrate considerable variation.<sup>7-17</sup> One variant of retrograde fast pathway conduction is distinguished by an abbreviated His-atrial (H-A) interval and minimal decremental conduction during ventricular pacing, with resistance to the drugs that suppress AV nodal conduction, such as adenosine, adenosine 5'-triphosphate (ATP), and verapamil.<sup>7-17</sup> Such "Kent bundle-like" properties of the retrograde fast pathway were considered to be the result of total bypass of the AV node, according to anatomic,<sup>18,19</sup> electrophysiologic,<sup>4-6,9-21</sup> and pharmacologic studies.<sup>7-17</sup> However, definitive evidence for participation of the atriohisian tract in typical AVNRT is lacking.<sup>22-24</sup>

The purposes of this study were (1) to assess the electrophysiologic properties of the retrograde fast pathway and response of the retrograde fast pathway to administration of ATP in patients with typical AVNRT, (2) to localize the lower turnaround site of the reentrant circuit, and (3) to elucidate the possible role of the concealed atriohisian tract in the genesis of the reentrant circuit of typical AVNRT.

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## Methods

### Patients

A total of 98 consecutive patients with typical (slow-fast form) AVNRT (30 men and 68 women, age  $49 \pm 19$  years) who underwent electrophysiologic study and slow pathway ablation were enrolled in this prospective study. Five patients (5%) had organic heart disease (3 old myocardial infarction, 1 dilated cardiomyopathy, 1 mitral regurgitation).

### Electrophysiologic study

The study protocol was reviewed and approved by the Institutional Committee on Human Research at the National Cardiovascular Center. Each patient gave written informed consent prior to the procedures. All antiarrhythmic drugs were discontinued for at least five half-lives prior to the procedure. With patients under local anesthesia, venous access was obtained from the femoral and antecubital veins to introduce five electrode catheters. Two quadripolar catheters were introduced from the femoral veins and positioned in the high right atrium and right ventricular (RV) apex. An octapolar catheter was introduced from the right antecubital vein and positioned inside the coronary sinus. A decapolar catheter (1-mm electrode width, 2-mm interelectrode spacing) was positioned across the tricuspid annulus for recording the most proximal His-bundle potential. An ablation catheter was introduced from the femoral vein and inserted into the right atrium for mapping and slow pathway ablation. Baseline electrophysiologic evaluation and tachycardia induction were performed during incremental pacing and extrastimulation [basic cycle length (CL): 500–700 ms] from the RV apex, high right atrium, and coronary sinus. Programmed electrical stimulation was performed using a programmable cardiac stimulator (EP-3 Computerized Stimulator, EP Med Systems, Inc., West Berlin, NJ, USA), with a pulse width of 2 ms and stimulus output of twice the pacing threshold. Bipolar electrograms were filtered through a bandpass of 30–500 Hz, displayed on a real-time monitor at a paper speed of 100 mm/s, and stored with 2-kHz sampling frequency on magneto-optical disks (Bard LabSystem Duo, Bard Electrophysiology, Lowell, MA, USA, or CardioLab, Prucka Engineering, Inc., Houston, TX, USA). Each electrophysiologic measurement was obtained twice using electrical calipers at a paper speed of 100 mm/s. A mean value was used for data analysis.

Exclusion of tachycardia mechanisms other than AVNRT and diagnosis of AVNRT were performed based upon classic criteria.<sup>25</sup> The absence of an AV accessory pathway was confirmed when ventricular preexcitation was absent during sinus rhythm and atrial pacing; the ventriculoatrial (VA) interval during the tachycardia was not lengthened by an occurrence of bundle branch block; the tachycardia was not reset by ventricular extrastimuli delivered while the His bundle was refractory; "parahisian pacing"<sup>26</sup> during sinus rhythm exhibited an exclusive retrograde AV nodal conduction pattern; and the VA interval during pacing from the RV apex was shorter than that during pacing from

the RV base. Atrial tachycardia was excluded when a "V-A-V sequence" (not a "V-A-A-V sequence") was observed upon cessation of ventricular pacing associated with 1:1 VA conduction during the tachycardia,<sup>27</sup> and the tachycardia was reproducibly terminated with ventricular extrastimuli not reaching the atrium. A diagnosis of AVNRT was made if an AV reentrant tachycardia using accessory pathways and atrial tachycardia was excluded by the above-mentioned criteria. Typical AVNRT was diagnosed when anterograde conduction occurred over the slow pathway with an atrio-His (A-H) interval during the tachycardia  $\geq 200$  ms, and retrograde conduction occurred over the fast pathway with earliest retrograde atrial activation at the right superoseptum.<sup>6</sup>

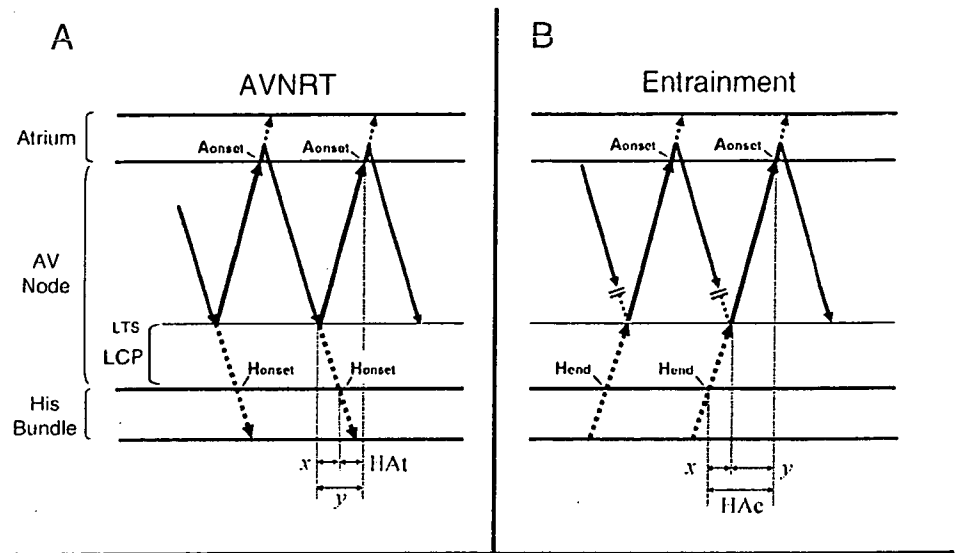
### Pharmacologic evaluation

After diagnosis of typical AVNRT, incremental doses of ATP (10, 20, 30, and 40 mg) were administered as intravenous boluses through a venous sheath in the inferior vena cava, followed by immediate saline flush, during pacing from the RV apex or parahisian RV region (400–600 ms) with stable 1:1 VA conduction over the retrograde fast pathway until retrograde fast pathway conduction block occurred. RV pacing was performed with a pacing CL shorter than the sinus CL but longer than the VA Wenckebach CL in each patient. Patients then received a bolus administration of the same dosage of ATP during stable sinus rhythm. Patients were divided into two groups according to the results of ATP testing during RV pacing: (1) ATP-S with transient VA block, and (2) ATP-R without VA block. Electrophysiologic data were compared between the groups. In both groups, maximal increments in the stimulus-atrial interval after ATP administration ( $\Delta SA_{ATP}$ , in milliseconds) were measured from the pacing stimulus to the earliest atrial electrogram recorded from the His-bundle catheter. Patients were excluded from data analysis if stable 1:1 conduction over the retrograde fast pathway was not present during RV pacing and/or ATP administration was contraindicated.

### Evaluation of conduction time over the lower common pathway

The conduction time over the lower common pathway was measured according to the previously reported hypothesis<sup>2–6</sup> after the diagnosis of typical AVNRT was made (Figure 1). When the conduction time over the lower common pathway was defined as  $x$  (in milliseconds) and that over the retrograde fast pathway (from the lower turnaround site to the earliest atrial activation site) as  $y$  (in milliseconds), the H-A interval during AVNRT (HAt, in milliseconds), as measured from the onset of the His-bundle potential recorded at the most proximal part of the His-bundle to the onset of the earliest atrial potential in the His-bundle recordings, would be the difference between them ( $HAt = y - x$ , Figure 1A). The H-A interval during entrainment pacing from the parahisian RV region without direct His-

**Figure 1** Concept of measurement of conduction time over the lower common pathway depicted by laddergrams showing activation sequences during AV nodal reentrant tachycardia (A) and ventricular pacing at the tachycardia rate (B), and the formulas used to calculate  $x$  (C). See text for details.  $A_{onset}$  = onset of earliest atrial activation;  $HAt$  and  $HAe$  = HA intervals during tachycardia and entrainment pacing from the parahisian right ventricular region at the tachycardia rate, respectively;  $H_{onset}$  and  $H_{end}$  = onset and end of the most proximal His-bundle electrogram, respectively; LCP = lower common pathway; LTS = lower turnaround site;  $x$  = conduction time over lower common pathway;  $y$  = conduction time over retrograde fast pathway.



bundle capture ( $HA_e$ , in milliseconds), as measured from the end of a His-bundle potential recorded at the most proximal portion of the His bundle to the onset of the earliest atrial potential in the His-bundle recordings, would be the sum of them ( $HA_e = y + x$ , Figure 1B). Entrainment pacing was performed from the parahisian RV region to separate the local ventricular electrogram from the His-bundle potential and clearly visualize the end of the His-bundle potential.<sup>3</sup> H-A intervals during the tachycardia and entrainment were measured from the onset and end of the most proximal His-bundle potential, respectively, because depolarization of the most proximal His bundle was considered to occur when a wavefront entered anterogradely and exited retrogradely from the most proximal portion of the His bundle during the tachycardia and entrainment, respectively. The formulas yield  $x = (HA_e - HA_t) / 2$  (Figure 1C). According to this hypothesis,  $x > 0$  suggests the presence of a lower common pathway between the lower turnaround site and His bundle;  $x = 0$  suggests the absence of a lower common pathway with the lower turnaround site at the junction between the distal AV node and proximal His bundle; and  $x < 0$  suggests the absence of a lower common pathway and a lower turnaround site within the His bundle. In the latter case, the retrograde fast pathway was considered to originate from the His bundle (atriohisian tract), and a part of the His bundle was considered to be involved in the reentrant circuit. Parahisian entrainment was performed by burst pacing from the distal bipole of the His-bundle catheter with a pacing output of twice the diastolic threshold of the local RV and a pacing CL 10–30 ms shorter than the tachycardia CL. Patients were excluded from data analysis if the tachycardia was not inducible at baseline, the tachycardia did not sustain during electrophysiologic evaluation, the tachycardia showed CL variability  $> 10$  ms, 1:1 stable

conduction over the retrograde fast pathway was absent during entrainment from the parahisian RV, and/or reliable electrophysiologic measurements of the and/or  $HA_t$  were not feasible because of unclear visualization of the His bundle and/or atrial potentials in the His-bundle electrogram.

**Slow pathway ablation**

Slow pathway ablation was performed at the conventional slow pathway region in the right inferoseptal area between the tricuspid annulus and ostium of the coronary sinus during sinus rhythm targeting the slow pathway potential.<sup>1</sup> Using a radiofrequency pulse generator (EPT 1000TC, Boston Scientific, Natick, MA, USA), a 550-kHz unmodulated current was delivered between the distal tip of a 4-mm-tip ablation catheter and indifferent patch electrode positioned on the patient's back in a temperature-controlled mode with target temperature 55–60°C, maximal power output 40 W, and duration  $\leq 60$  seconds for each application. Inducibility of AVNRT was assessed after each application. Successful slow pathway ablation was defined as elimination of a jump-up ( $\geq 50$  ms) in the A2-H2 interval in response to 10-ms decrements in the A1-A2 interval or induction of single AV nodal echo beats for at least 30 minutes after the last energy application with and without an isoproterenol infusion.<sup>1</sup>

**Statistical analysis**

All continuous variables are expressed as mean  $\pm$  SD. Student's t-test was used to compare unpaired variables between patient groups. Fisher's exact probability test was used to compare categorical variables between patient groups.  $P < .05$  was considered significant.

Table 1 Electrophysiologic data

	ATP-S [n = 47 (63.5%)]	ATP-R [n = 27 (36.5%)]	P value
Ant-WCL	327 ± 38	317 ± 28	NS
Retro-WCL	306 ± 22	297 ± 14	NS
Ant-ERP <sub>AVN</sub>	241 ± 31	247 ± 27	NS
Retro-ERP <sub>AVN</sub>	NA	NA	—
ΔH1A1	35 ± 33	2 ± 2	<.05
ΔH2A2	3 ± 2	2 ± 1	NS
TCL	350 ± 42	355 ± 41	NS
HAt	38 ± 17	51 ± 18	<.05
HAe	46 ± 16	39 ± 17	NS
x	4 ± 4	-6 ± 5	<.05
x > 0	41 patients (87%)	2 patients (7.5%)	<.01
x = 0	4 patients (9%)	2 patients (7.5%)	
x < 0	2 patients (4%)	23 patients (85%)	
ΔSA <sub>ATP</sub>			
≤ 5 ms	31 patients (66%)	27 patients (100%)	
> 5 ms	16 patients (37%)	0 patient (0%)	
	14 ± 6		
Total	6 ± 7	3 ± 2	NS

Values are given in milliseconds, unless otherwise indicated.

Ant-ERP<sub>AVN</sub> and Retro-ERP<sub>AVN</sub> = effective refractory period of anterograde and retrograde atrioventricular nodal conduction, respectively; Ant-WCL and Retro-WCL = Wenckebach cycle length of anterograde and retrograde atrioventricular nodal conduction, respectively; HAe and TCL = tachycardia cycle length; HAt = HA interval during ventricular entrainment and tachycardia; x = (HAe - HAt)/2; ΔH1A1 = maximal increment of H1A1 interval during burst ventricular pacing; ΔH2A2 = maximal increment of H2A2 interval during ventricular extrastimulation; ΔSA<sub>ATP</sub> = maximal increment of stimulus-atrium interval after ATP bolus.

## Results

Among the 98 patients enrolled in this study, 24 (24%) patients were excluded from data analysis because of contraindications to ATP (2 patients), inability to induce AVNRT at baseline (10 patients), tachycardia CL variation >10 ms (5 patients), and unclear recording of the retrograde His-bundle potential during parahisian entrainment (7 patients). The remaining 74 (76%) patients (24 men and 50 women, age 50 ± 17 years) were included in data analysis (Table 1).

### ATP sensitivity of the AV nodal pathways

All 74 patients received an intravenous bolus of ATP 24 ± 13 mg (0.5 ± 0.2 mg/kg) during both RV pacing with 1:1 stable retrograde fast pathway conduction (pacing CL: 509 ± 33 ms) and sinus rhythm with 1:1 AV nodal conduction (sinus CL: 877 ± 118 ms) after the diagnosis of typical AVNRT was made. During RV pacing, 47 patients developed transient VA block after the bolus of ATP (dose: 16 ± 6 mg, 0.3 ± 0.3 mg/kg; ATP-S: 63.5%), whereas the other 27 patients did not develop transient VA block after the 40-mg bolus of ATP (0.8 ± 0.1 mg/kg; ATP-R: 36.5%). Among the ATP-S patients, ΔSA<sub>ATP</sub> was ≤ 5 ms in 31 (66%) patients and was > 5 ms in the remaining 16 (37%) patients. On the other hand, ΔSA<sub>ATP</sub> was ≤ 5 ms in all 27 ATP-R patients. Mean ΔSA<sub>ATP</sub> did not differ statistically between the groups (ATP-S vs ATP-R: 6 ± 7 ms vs 3 ± 2 ms, P >.05; Table 1). All 74 patients had transient A-H block after bolus of the same dose of ATP during sinus rhythm (not shown).

### Electrophysiologic measurements

The results of electrophysiologic measurements are summarized in Table 1. Each electrophysiologic measurement was reproducible, with measurement error of <5 ms. No patient had ventricular preexcitation, and A-H and His-ventricular (H-V) intervals during sinus rhythm were normal in all patients at baseline. There was no significant difference in anterograde (Ant-WCL) and retrograde AV nodal Wenckebach CLs (Retro-WCL) and effective refractory period of the anterograde AV nodal conduction (Ant-ERP<sub>AVN</sub>). Determination of the effective refractory period of the retrograde fast pathway (Retro-ERP<sub>AVN</sub>) was prevented by the decremental properties of the retrograde ventricle-His bundle conduction<sup>14</sup> and refractory period of the local RV during ventricular extrastimulation. Maximal increment in the H-A interval during burst RV pacing was significantly longer in ATP-S than in ATP-R (ΔH1A1: 35 ± 33 ms vs 2 ± 2 ms, P <.05), suggesting decremental and nondecremental properties of the retrograde fast pathway in ATP-S and ATP-R, respectively. Maximal increment in the H-A interval during ventricular extrastimulation (ΔH2A2) did not differ between the groups, possibly because of the relatively constant H1-H2 interval caused by decremental V2-H2 conduction (not shown).<sup>14</sup> Mean tachycardia CL, HAt, HAe and x were 352 ± 42 ms, 43 ± 17 ms, 43 ± 16 ms, and 0 ± 5 ms, respectively. HAt was significantly longer and x significantly shorter in the ATP-R group than in the ATP-S group (HAt: 51 ± 18 ms vs 38 ± 17 ms, P <.05, x: -6 ± 5 ms vs 4 ± 4 ms, P <.05; Table 1, and Figures 2 and 3). There was no significant difference in the tachycardia CL and HAe between groups. x was <0 ms in 23 (85%) of 27 ATP-R patients, suggesting that the concealed atriohisian tract could partic-