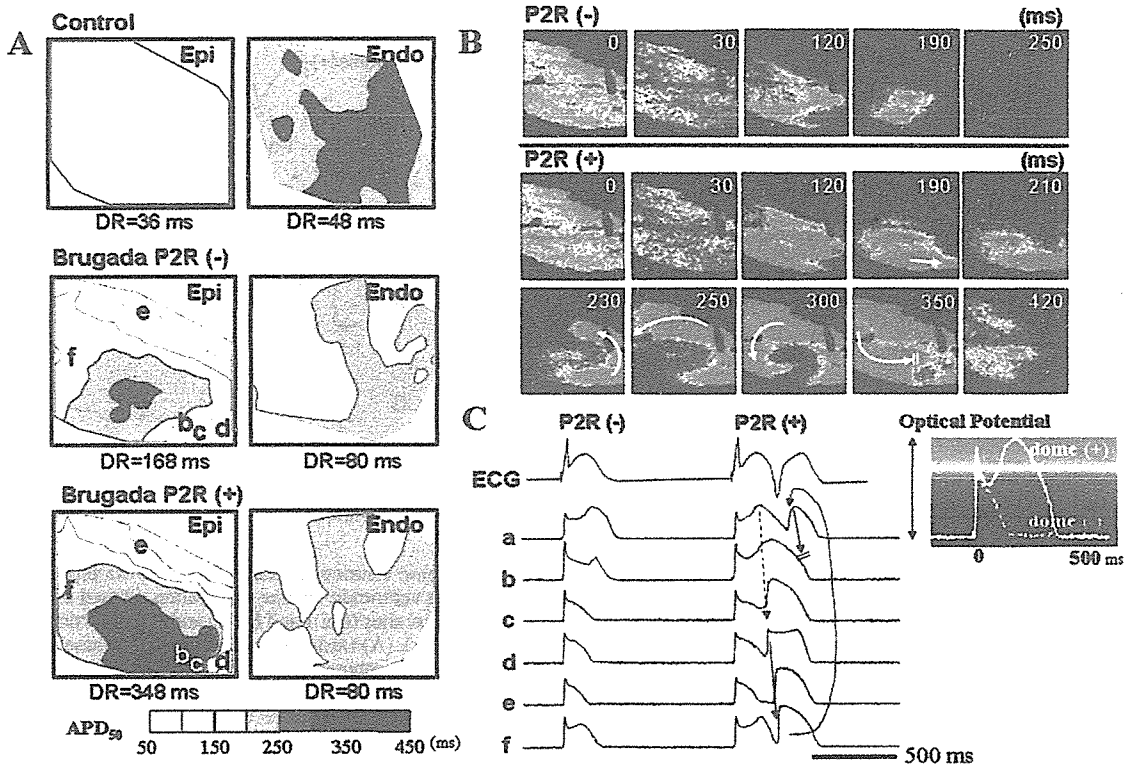

Fig 3. Mechanism of the phase 2 reentry-induced premature beats (P2R-extrasystoles) under the condition of Brugada-ECG in a model using a wedge preparation combined with high-resolution (256×256) optical mapping techniques. (A) Representative action potential duration measured at 50% (APD_{50}) contour map on the right ventricular epicardium (Epi) and endocardium (Endo) in the control, in the ST-segment elevation (Brugada-ECG) without phase 2 reentrant extrasystoles (P2R (–)) and in the Brugada-ECG just before P2R extrasystoles (P2R (+)). (B) Snapshots of an optical isopotential movie on the Epi surface during P2R(–) and P2R(+) in the Brugada-ECG. (C) Optical action potentials (APs) at each site (a–f) on the Epi surface and transmural ECG. Under the Brugada-ECG, the AP morphology in Epi, but not Endo, changes to heterogeneous because of the combination of abbreviated (loss-of-dome; site d,e) and prolonged (restore-of-dome; site a,b) APs, resulting in increasing dispersion of repolarization (DR) in Epi (168 ms) rather than in Endo (80 ms). Further prolongation of the AP in the Epi area (site b) is closely adjacent to the loss-of-dome APs (site d), thus producing a repolarization mismatch within a small area (DR = 348 ms) and developing a P2R-extrasystole at the loss-of-dome site (site d). Thus, a steep repolarization gradient in Epi, but not in Endo, develops the initial P2R-extrasystole in the Brugada-ECG (Modified from *J Am Coll Cardiol* 2006; **47:** 2074–2085 with permission).

sodes of VF than in those of polymorphic VT. Figs 4A,B represents a phase map and the optical APs during the P2R-induced polymorphic VT, showing that reentry is initiated from the epicardial GR_{max} area and rotates mainly in the epicardium without wave-break. In contrast, Figs 5A,B represents these during P2R-induced VF, showing that the development of the initial P2R is similar to that of polymorphic VT, but that the first P2R-wave is broken up into multiple wavelets, resulting in degeneration of VT into VF. The phase singularity points during the first P2R-wave almost coincide with the sites of delayed conduction (Fig 5D). Wave-break during the first P2R-extrasystole produces multiple wavelets in the episodes of VF, whereas no wave-break or wave-break followed by wave collision and termination occurs in the episodes of polymorphic VT. Figs 4E and 5E are histograms of the epicardial APD measured at 50% (APD_{50}) during the first P2R-wave. There is a large variety of APD_{50} in the epicardium during the first P2R-wave in the episodes of VF, whereas only slight variety in the APD_{50} is observed in the episodes of polymorphic VT. These data suggest that both conduction delay and dispersion of repolarization play significant roles in the perpetuation of VF episodes.

Late Onset of Clinical Manifestation

Because BS is a primary electrical disease, and at least one-third of the patients have mutations in ion channel genes (*SCN5A*, *CACNA1C*, *CACNB2*), clinical manifestation during childhood would be expected. However, BS usually manifests in middle age, at 40–50 years of age? Frustaci et al recently reported a significant myocytes apotosis in both the right and left ventricular myocardium in a histological study of BS patients with *SCN5A* mutations, and suggested that abnormal function of the sodium channels may lead to a sufficient degree of cellular damage, attributing to the arrhythmic event?[28] We recently analyzed several ECG parameters recorded during long-term follow-up of BS patients with and without the *SCN5A* mutation?[29] In both patient groups, the depolarization parameters, including P wave, QRS, S wave duration and PQ interval, increased with age, especially in patients with the *SCN5A* mutation. Taken together with the experimental data?[27] the findings suggest that depolarization abnormalities (conduction slowing) are required for the maintenance of VF in BS, although the initiating premature beats are caused by a phase 2 reentry mechanism.

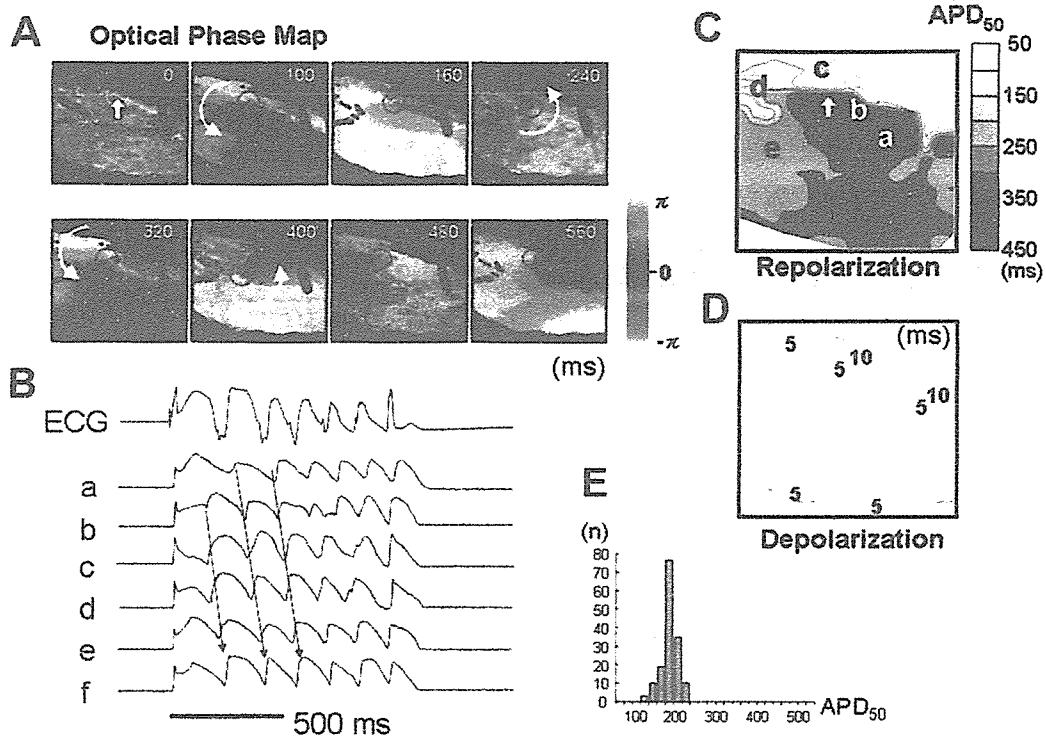

Fig4. Mechanism underlying non-sustained polymorphic ventricular tachycardia (VT) in a Brugada model using a wedge preparation combined with high-resolution (256×256) optical mapping techniques. (A) Representative snapshots from a phase movie during polymorphic VT originating from epicardial (Epi) phase 2 reentry (P2R). (B) Optical action potentials at each site (a–f), together with a transmural ECG. (C, D) Repolarization and depolarization maps on the Epi surface in the condition of Brugada-ECG just before polymorphic VT. (E) Epi action potential duration at 50% repolarization (APD_{50}) histogram during the first P2R-wave. Reentry is initiated from the steepest (maximum) repolarization gradient site in Epi (arrow in A and C) and rotates mainly in Epi without wave-break. The Epi depolarization map paced from Endo shows no conduction delay (D). There is a little variety of APD in Epi during the first P2R-wave (E). Open circles mark phase singularity points (Modified from *J Am Coll Cardiol* 2006; **47:** 2074–2085 with permission).

Male Predominance

Because all mutations so far identified in *SCN5A* display an autosomal dominant mode of transmission in BS, males and females would be expected to inherit the defective gene equally. However, an apparent male predominance is observed in patients with BS[15] Di Diego et al suggested the cellular basis for male predominance in BS while using arterially-perfused canine RV wedge preparations[30] They reported that the I_{to}-mediated phase 1 AP notch in the RV epicardium was larger in male dogs than in female dogs was responsible for the male predominance in the Brugada phenotype. On the other hand, the male hormone, testosterone, has been reported to increase the outward potassium currents (the rapidly [I_{Kr}][31,32] and the slowly [I_{Ks}][33] activating component of I_K, and the inward rectifier potassium current [I_{K1}][32]) or decrease the inward currents ($I_{Ca\text{-}L}$)[33] Therefore, testosterone would be expected to accentuate the Brugada phenotype. Clinically, Matsuo et al report 2 cases of asymptomatic BS in which typical coved ST-segment elevation disappeared following orchiectomy as therapy for prostate cancer[34] supporting the expectation for testosterone. Moreover, testosterone is also known to decrease visceral fat[35] and patients with BS are thinner than the normal population[36] On the basis of these clinical and experimental findings, we directly measured the testosterone level in male patients with BS and compared them with age-matched normal males[37] The testosterone level was significantly higher and body mass index (BMI) significantly lower in the Brugada males than in the controls after adjusting for several confounding variables influencing testosterone level or BMI (eg, age, exercise, stress, smoking, and medication). Interestingly, testosterone level was inversely correlated with BMI in both Brugada and control males even after adjusting for confounding variables, suggesting that Brugada males have a higher testosterone level associated with lower visceral fat (Fig6). Moreover, conditional logistic regression model analysis showed that both higher testosterone level and lower BMI independently increase the risk of BS. These data suggest that the male predominance in the Brugada phenotype is at least in part related to testosterone, which is present only in males.

Higher Incidence in Asian Population

The incidence of BS is higher in Asian countries, including Thailand and Japan, than in Western countries[1,11,12,38] It has been reported that common polymorphisms might modulate the activity of the primary disease-causing mutation or influence susceptibility to arrhythmia, even in the general population[39] The common polymorphisms may attribute to ethnic differences in the clinical phenotype in inherited cardiac arrhythmias, including BS, because some common polymorphisms are ethnically dependent. Pfeufer et al reported that polymorphisms in the *SCN5A* promoter were associated with a widening of QRS duration in a cen-

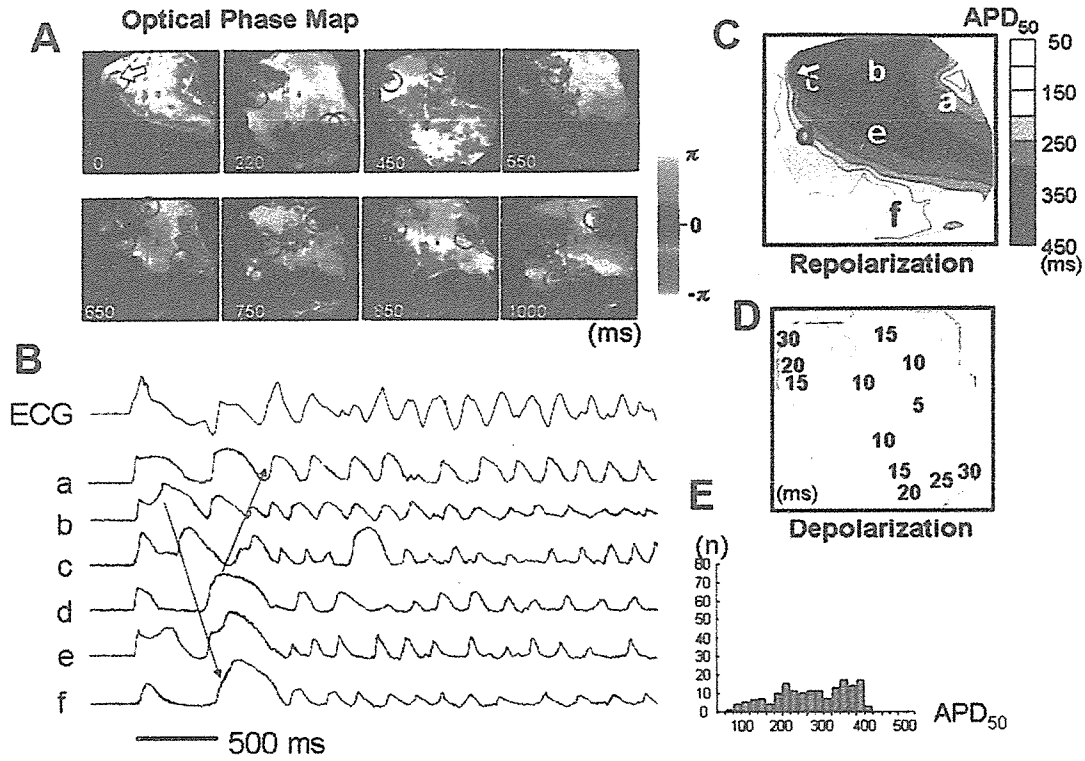

Fig 5. Mechanism underlying ventricular fibrillation (VF) in a Brugada model using a wedge preparation combined with high-resolution (256×256) optical mapping techniques. (A) Representative snapshots from a phase movie during VF originating from the epicardial (Epi) phase 2 reentry (P2R). (B) Optical action potentials at each site (a–f), together with a transmural ECG. (C, D) Repolarization and depolarization maps on the Epi surface in the condition of Brugada-ECG just before VF. (E) Epi action potential duration at 50% repolarization (APD_{50}) histogram during the first P2R-wave. The area of maximum gradient of repolarization in Epi (arrow in A and C) develops the P2R. The first P2R-wave is broken up into multiple wavelets (A, 220 ms), resulting in degeneration of ventricular tachycardia into VF. The Epi depolarization map paced from the endocardium shows a remarkable conduction delay in the episode of VF (D). The phase singularity points during the first P2R-wave (open circle in D) almost coincide with the Epi sites of delayed conduction. There is a large variety of APD in Epi during the first P2R-wave (E). Thus, P2R-extrasystoles degenerate into VF with further depolarization and repolarization disturbances. Open circles mark phase singularity points (Modified from *J Am Coll Cardiol* 2006; **47**: 2074–2085 with permission).

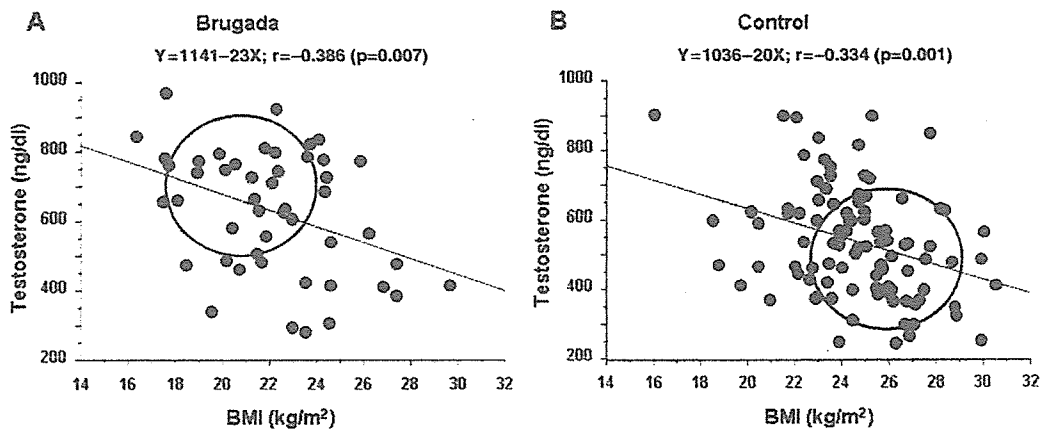

Fig 6. Correlation between testosterone level and body mass index (BMI) in Brugada syndrome males and age-matched control males. Testosterone level inversely correlated withe BMI in both groups (*J Cardiovasc Electrophysiol* 2007 (in press), with permission).

tral European general population[40] We recently identified a haplotype variant consisting of 6 individual DNA polymorphisms in near-complete linkage disequilibrium within the proximal promoter region of *SCN5A* in Asians only (an allele frequency of 22%), not in Caucasian or African-Americans (Fig 7)[41] Luciferase reporter activity of this variant haplotype, designated Haplotype B, in cardiomyocytes is reduced 62% compared with the wild-type, designated Haplotype A. To test the hypothesis that this *SCN5A* promoter polymorphism may modulate variability in cardiac

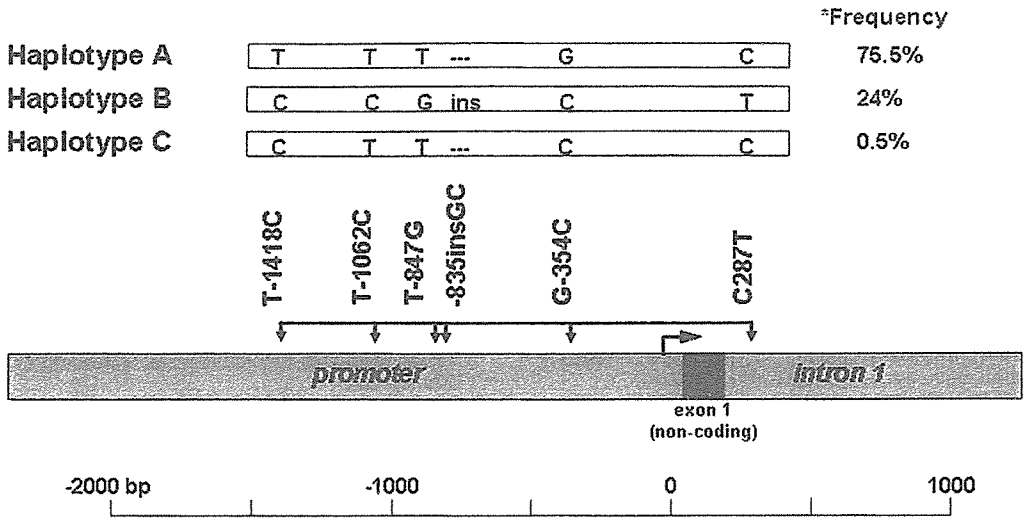

Fig 7. Haplotypes identified within the proximal promoter region of *SCN5A*, a cardiac sodium-channel gene. The 6 polymorphisms are in near-complete linkage disequilibrium. Haplotype A is designated as containing all common alleles, and Haplotype B as containing all minor alleles. The discordant haplotype is designated Haplotype C. *Frequency in the Japanese (control) population (Modified from *Circulation* 2006; **113:** 338–344 with permission).

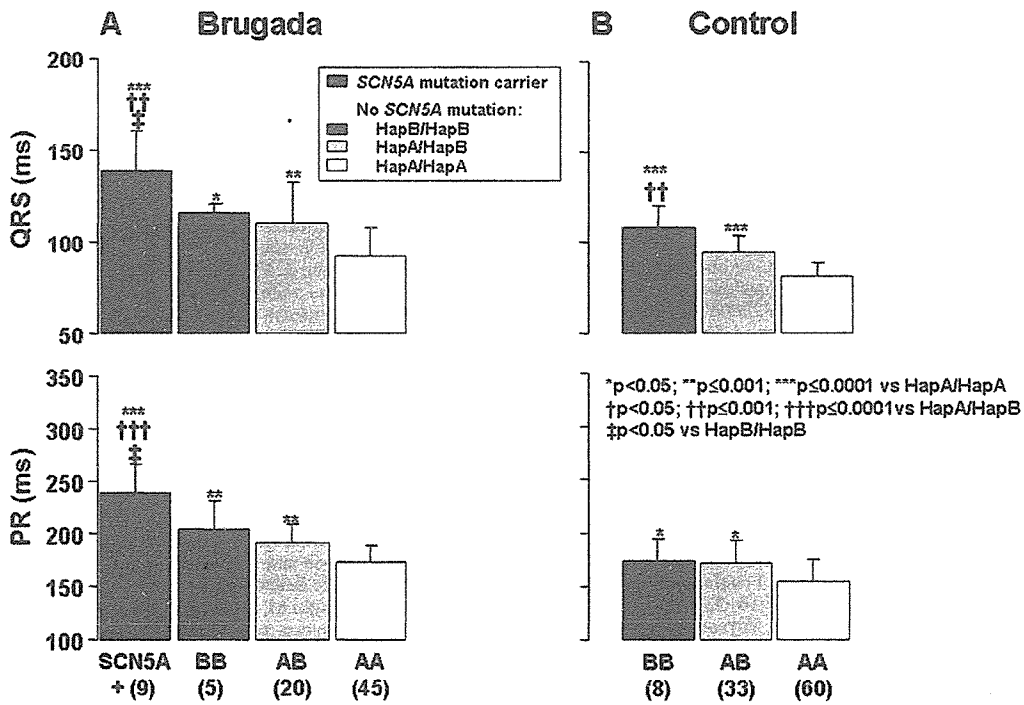

Fig 8. *SCN5A* promoter haplotype pair effects on QRS duration in lead V_6 and PR duration in lead II in patients with Brugada syndrome and in control subjects. In the Brugada patients without *SCN5A* mutations and in the control subjects, both QRS and PR duration show a gene–dose effect, being longest in Haplotype B homozygotes (BB), intermediate in Haplotype A/Haplotype B heterozygotes (AB) and shortest in Haplotype A homozygotes (AA). The Brugada patients with *SCN5A* mutations show the longer duration of both QRS and PR than do those without *SCN5A* mutations. Patient numbers are indicated between parentheses. Data mean±SD (Modified from *Circulation* 2006; **113:** 338–344 with permission).

conduction, the relationship between the *SCN5A* promoter haplotype and indices of conduction velocity (ie, PR and QRS durations) was analyzed in a cohort of 71 Japanese BS subjects without *SCN5A* mutations and in 102 Japanese controls. In both groups, PR and QRS durations were significantly longer in Haplotype B individuals, with a gene–dose effect (Fig 8). Moreover, increases in both the PR and QRS duration with sodium channel blockers, which are known to be arrhythmogenic in BS, were genotype-dependent and a gene–dose effect was also observed. These data demonstrate that the Haplotype B within the *SCN5A* promoter region alone does not give rise to BS, but that it likely contributes to a higher incidence of BS in Asian population in combination with other yet unknown (genetic) factors.

Acknowledgments

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Diagnostic and Prognostic Value of a Type 1 Brugada Electrocardiogram at Higher (Third or Second) V_1 to V_2 Recording in Men With Brugada Syndrome

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To evaluate the diagnostic and prognostic value of an electrocardiogram (ECG) recorded at a higher (third or second) intercostal space, 98 men (17 to 76 years of age, mean ± SD 47 ± 13; with documented ventricular fibrillation [VF] in 22 and syncope in 32) were categorized into 3 groups; 68 men had a spontaneous type 1 ECG in standard leads V_1 and V_2 (S group), 19 had a spontaneous type 1 ECG only in the higher V_1 and V_2 leads (H group), and 11 had a type 1 ECG only after receiving class Ic sodium channel blockers (Ic group). There were no significant differences in baseline clinical characteristics, including VF episodes, syncope, atrial fibrillation, family history, late potentials, and inducibility of VF during electrophysiologic study across the 3 groups. During prospective follow-up periods (779 ± 525, 442 ± 282, and 573 ± 382 days, respectively), subsequent cardiac events occurred in 11 men (16%) within the S group, in 2 men (11%) in the H group, and in 0 men (0%) in the Ic group (p = NS, S vs H group). In men with previous episodes of VF, subsequent cardiac events occurred in 7 (44%) within the S group and in 2 (50%) in the H group (p = NS). In conclusion, men with a spontaneous type 1 Brugada ECG recorded only at higher leads V_1 and V_2 showed a prognosis similar to that of men with a type 1 ECG in using standard leads V_1 and V_2. (Am J Cardiol 2007;99:53–57)

Brugada syndrome is characterized by a high risk of sudden cardiac death due to ventricular fibrillation (VF) and a specific ST-segment elevation in the right precordial leads (V_1 to V_3) in the absence or presence of sodium channel blockers.[1,2] Recent consensus reports have proposed 3 types of ST-segment elevation (types 1 to 3) in this syndrome.[3–5] Although the magnitude and pattern of ST-segment elevation differ in each patient and can change even in the same patient,[6–8] documentation of a spontaneous type 1 electrocardiogram (ECG), which is defined as a coved type and a J-point elevation ≥0.2 mV, has been associated with a high risk of sudden cardiac death.[3–5,9–11] Electrocardiographic recording in leads V_1 and V_2 at a higher (third or second) intercostal space has been reported to unmask or confirm a type 1 Brugada ECG, with a high sensitivity in individuals with suspected Brugada syndrome.[12–14] However, systematic evaluation of recording leads V_1 and V_2 at a higher space, especially with regard to diagnostic and prognostic values, has not been done. This study evaluated the diagnostic and prognostic value of documentation of a spontaneous type 1 Brugada ECG in leads V_1 and V_2 recorded at a higher intercostal space.

Methods

The study population consisted of 98 probands from 98 unrelated families in whom a type 1 Brugada ECG was documented in leads V_1 and V_2 at a standard (fourth) and/or higher (third or second) intercostal space in the absence or presence of class Ic sodium channel blockers. They were enrolled between October 2000 and September 2004 and were followed prospectively. All 98 patients were men. Their average age at enrollment was 47 ± 13 years (17 to 76). VF had been documented in 22 men and 32 had shown only syncope. An SCN5A coding region mutation was identified in 8 men. Physical examination showed no abnormal findings, and no evidence of structural heart disease was demonstrated by echocardiogram in any subject. Informed consent was obtained from all subjects.

The 98 men were categorized into 3 groups; 68 had a spontaneous type 1 Brugada ECG recorded at a standard (fourth) intercostal space in leads V_1 and V_2 (S group), 19 had a spontaneous type 1 Brugada ECG recorded only at a higher (third or second) intercostal space in leads V_1 and V_2 (H group), and 11 had a type 1 Brugada ECG recorded only

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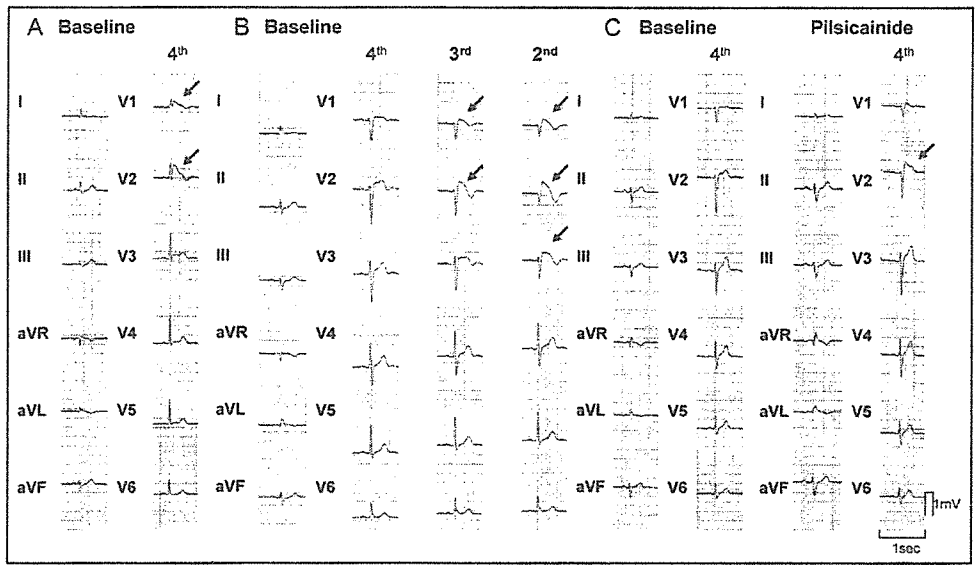

Figure 1. Twelve-lead ECG in representative subjects of the 3 groups. *(A)* S group (spontaneous). A type 1 coved-type ST-segment elevation was seen at a standard (fourth) intercostal space in leads V_1 and V_2 *(arrows)* at baseline. *(B)* H group (spontaneous). A type 1 Brugada ECG was recorded at higher (third and second) intercostal spaces in leads V_1 and V_2 (V_3) *(arrows)* but not at a standard (fourth) intercostal space in these leads at baseline. *(C)* Ic group. A type 1 Brugada ECG was recorded at a standard (fourth) intercostal space in leads V_2 only after injection of 30 mg of pilsicainide.

Table 1
Comparison of clinical, electrocardiographic, and electrophysiologic characteristics across the 3 groups (S group vs H group vs Ic group)

Variable	S Group (only spontaneous) (n = 68)	H Group (only spontaneous) (n = 19)	Ic Group (n = 11)	p Value
Age (yrs) (range)	48 ± 16 (21–76)	46 ± 15 (17–72)	44 ± 16 (17–62)	0.64
Symptomatic	40 (59%)	7 (37%)	7 (64%)	0.20
Documented VF	16 (24%)	4 (21%)	2 (18%)	0.91
Syncope only	24 (35%)	3 (16%)	5 (45%)	0.17
Inducible VF/ventricular tachycardia	42 (78%)	6 (55%)	7 (70%)	0.27
Family history	14 (21%)	2 (11%)	3 (27%)	0.48
Presence of late potential	46 (74%)	11 (65%)	6 (55%)	0.59
Presence of atrial fibrillation	16 (24%)	3 (16%)	1 (9%)	0.47
Follow-up (d)	779 ± 525	442 ± 282	573 ± 382	<0.01*

* S group versus H group.

after receiving class Ic sodium channel blockers at standard and/or higher spaces in leads V_1 and V_2 (Ic Group) (Figure 1). We compared clinical, electrocardiographic, and electrophysiologic characteristics, and subsequent occurrence of cardiac events across the 3 groups.

Twelve-lead electrocardiographic data were recorded at a paper speed of 25 mm/s during sinus rhythm in a supine state at rest. Leads V_1 and V_2 were recorded at standard (fourth) and higher (third and second) intercostal spaces. At enrollment and categorization of subjects into 3 groups, ≥3 separate recordings of 12-lead ECGs were reviewed in each subject. If a spontaneous type 1 Brugada ECG was recorded at a standard space in leads V_1 and V_2 ≥1 time among multiple ECGs, the subject was classified into the S group. Similarly, if a spontaneous type 1 Brugada ECG was recorded at a higher space in leads V_1 and V_2 ≥1 time but not at all in standard leads V_1 and V_2, the subject was classified into the H group.

Drug challenge testing was performed with intravenous pilsicainide (1 mg/kg, maximum 50 mg, 5 mg/min) and/or flecainide (2 mg/kg, maximum 100 mg, 10 mg/min). The test result was considered positive if a type 1 Brugada ECG appeared in >1 precordial lead.

Late potential was analyzed using a signal-averaged electrocardiographic system (Arrhythmia Research Technology 1200EPX, Milwaukee, Wisconsin). 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, and (3) duration of low-amplitude signals <40 μV of the filtered QRS complex. Late potential was considered present when a root-mean-square voltage <18 μV and a duration >38 ms were present.

An electrophysiologic study was conducted without antiarrhythmic drugs after informed consent was obtained. Programmed electrical stimulation was performed from the right ventricular apex and the right ventricular outflow tract with up to 3 extrastimuli. Induction of VF requiring direct cardioversion or nonsustained polymorphic ventricular tachycardia lasting ≥15 beats was considered a positive result.

All men were followed up at outpatient clinics of the National Cardiovascular Center. The end point was VF

documented in the storage memory of an implantable cardioverter-defibrillator, apparent syncope, or sudden cardiac death.

Quantitative values were expressed as mean ± SD. Statistical significance in differences was analyzed by chi-square test or 1-way analysis of variance across the 3 groups (S vs H vs Ic group). A p value <0.05 was considered statistically significant. Survival curves were plotted using Kaplan-Meier methods and analyzed by log-rank test.

Results

Table 1 presents a comparison of clinical, electrocardiographic, and electrophysiologic characteristics across the S group (spontaneous only), H group (spontaneous only), and Ic group. There were no significant differences in baseline clinical characteristics with respect to gender, age, frequency of documented episodes of VF and syncope, family history (sudden cardiac death or a Brugada ECG), late potential, atrial fibrillation, and inducibility of VF/ventricular tachycardia during the electrophysiologic study across the 3 groups.

In all 68 men in the S group, a spontaneous type 1 Brugada ECG was always seen at a higher space in leads V_1 and V_2 on all ECGs showing a spontaneous type 1 Brugada ECG at a standard space in leads V_1 and V_2. Ten of 68 men (15%) in the S group always showed a type 1 Brugada ECG at a standard space in leads V_1 and V_2 on multiple ECGs. However, the remaining 58 men (85%) did not always show a type 1 Brugada ECG at a standard position, and 30 of these (52%) always showed a type 1 Brugada ECG at a higher space in leads V_1 and V_2. Of the 19 men in the H group, 7 (37%) always showed a type 1 Brugada ECG at a higher space in leads V_1 and V_2. In the 11 patients in the Ic group, 8 (73%) showed a type 1 Brugada ECG after class Ic drugs at a standard space in leads V_1 and V_2, and 3 (27%) showed this only at a higher space in leads V_1 and V_2.

An implantable cardioverter-defibrillator was implanted in 47 of the 68 subjects (69%) in the S group (VF in 14 of 16, 88%; syncope only in 19 of 24, 79%; asymptomatic in 14 of 28, 50%), in 7 of the 19 subjects (37%) in the H group (VF in 4 of 4, 100%; syncope only in 1 of 3, 33%; asymptomatic in 2 of 12, 17%), and 7 of the 11 subjects (64%) in the Ic group (VF in 2 of 2, 100%; syncope only in 3 of 5, 60%; asymptomatic in 2 of 4, 50%). Three subjects (4%) in the S group and 1 (5%) in the H group were treated with antiarrhythmic drugs only (2 with amiodarone and 1 with disopyramide in the S group and 1 with atenolol in the H group).

The mean prospective follow-up period was 779 ± 525 days in the S group, 442 ± 282 days in the H group, and 573 ± 382 days in the Ic group. The follow-up period was significantly longer in the S group than in the H group ($p<0.01$; Table 1). This difference was explained by the fact that more men were enrolled unintentionally in the S group soon after the prospective study was started.

Kaplan-Meier analysis of subsequent cardiac events during follow-up in the 3 groups is shown in Figure 2.

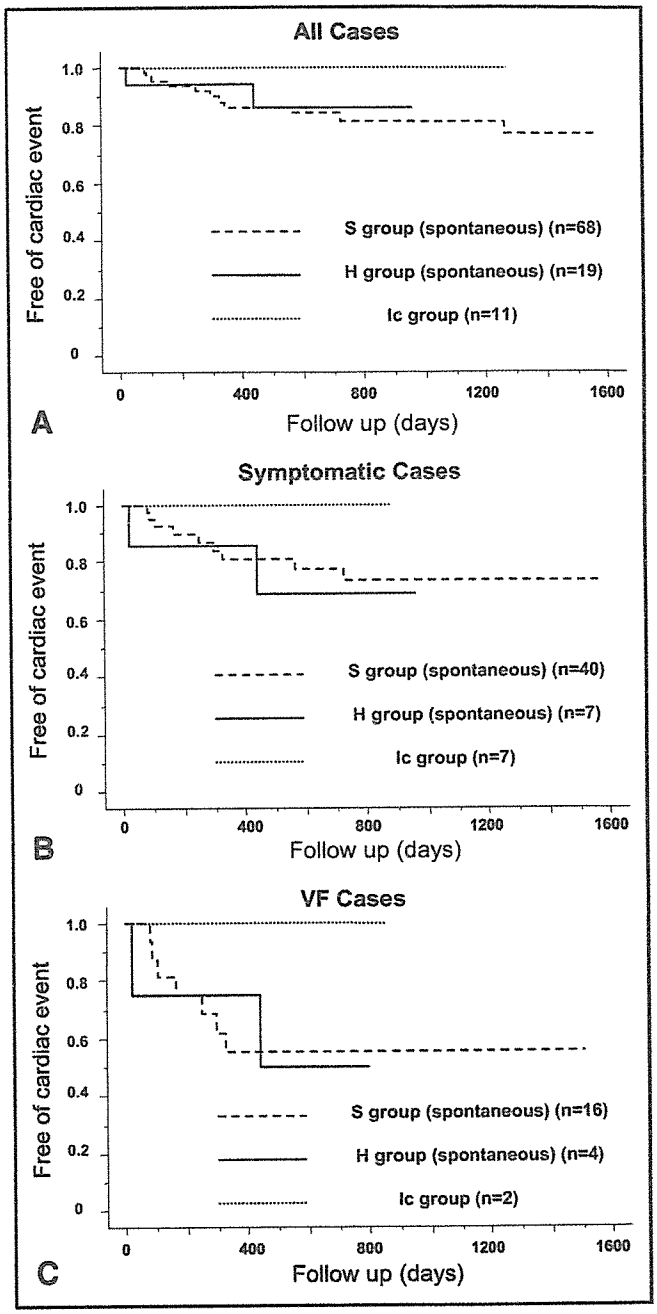

Figure 2. Kaplan-Meier analysis of subsequent cardiac events (VF in implantable cardioverter-defibrillator storage or sudden cardiac death) in the S group (spontaneous) *(dashed line)*, H group (spontaneous) *(solid line)*, and Ic group *(dotted line)* for *(A)* all patients, *(B)* symptomatic patients with previous VF and/or syncope, and *(C)* patients with previously documented VF.

Subsequent cardiac events occurred in 11 of 68 subjects (16%) in the S group (VF in implantable cardioverter-defibrillator storage in 9, sudden cardiac death in 2), 2 of 19 subjects (11%) in the H group (VF in implantable cardioverter-defibrillator storage in 2), but 0 of 11 subjects (0%) in the Ic group (Figure 2). No significant difference was observed in the frequency of cardiac events between the S and H groups.

Of the 13 men with subsequent cardiac events, 9 (69%) had previous VF (7 in the S group, 2 in the H group), 2 (15%) had previous syncope only (2 in the S group), and 2 (15%) were asymptomatic (2 in the S group) at enrollment. Because previous VF and/or syncope are strong indicators of subsequent cardiac events,[9,10,15] the frequency of subsequent cardiac events was evaluated when the subjects were limited to symptomatic patients with previous VF and/or syncope. No significant difference was observed in the frequency of subsequent cardiac events between 40 symptomatic subjects in the S group and 7 symptomatic subjects in the H group (23%, 9 of 40, vs 29%, 2 of 7; Figure 2).

When the subjects were limited to patients with previous VF (16 in the S group, 4 in the H group), there was no significant difference in the frequency of subsequent cardiac events between the 2 groups (44%, 7 of 16, vs 50%, 2 of 4; Figure 2).

Of the 19 subjects in the H group, 14 underwent a drug challenge test, and 2 showed a type 1 Brugada ECG at a standard space in leads V_1 and V_2 after the test.

Discussion

The major findings of our study were that (1) recording at a higher space in leads V_1 and V_2 had higher sensitivity than that at a standard space in these leads in detecting a type 1 Brugada ECG and (2) a type 1 Brugada ECG recorded only at a higher space in leads V_1 and V_2 showed a similar prognostic value for subsequent cardiac events as that recorded at a standard space in these leads.

Priori et al[9] reported that only 50% of patients with Brugada syndrome in whom repetitive baseline ECGs were recorded had $\geq$1 positive baseline ECG. In the present study, only 10 of 68 subjects (15%) in the S group always showed a type 1 Brugada ECG at a standard space with leads V_1 and V_2. Because a region reflecting the potentials of the right ventricular outflow tract includes higher precordial ECGs (second or third in leads V_1 and V_2), we hypothesized that recordings at a higher space in leads V_1 and V_2 would detect a type 1 coved-type Brugada ECG more frequently in patients with Brugada syndrome and transient ST-segment elevation. Shimizu et al[12] used body surface potential mapping and examined the body surface distribution of maximum (coved type) ST-segment elevation in patients with Brugada syndrome in whom spontaneous coved type ST-segment elevation was documented $\geq$1 time in the standard leads V_1 and V_2. They reported that the maximum ST-segment elevation was distributed at row 5 of the body surface potential mapping, on which leads V_1 and V_2 on standard ECG were located, in 18 of 25 patients (72%) with Brugada syndrome and at row 6, which was on the level of parasternal second intercostal space, in the remaining 7 patients (28%) with Brugada syndrome. In the latter patients, typical coved type ST-segment elevation was recognized only at a higher (third or second) space in leads V_1 and V_2 on the standard 12-lead ECG.

In the present study, the remaining 58 of 68 subjects (85%) in the S group did not always show a type 1 Brugada ECG on standard leads V_1 and V_2; however, 30 of 58 subjects (52%) always showed a type 1 Brugada ECG on the higher leads V_1 and V_2, suggesting that a higher electrocardiographic recording has higher sensitivity for detecting a type 1 Brugada ECG, as in previous studies.[12–14] Moreover, higher recordings in leads V_1 and V_2 showed similar prognostic value as standard recordings in these leads. Because recordings of leads V_1 and V_2 at a higher (third or second) intercostal space are easy and noninvasive procedures, we recommend the higher recordings in leads V_1 and V_2 as an alternative to drug challenge testing with sodium channel blockers. Only when the result of this procedure is negative should a drug challenge test be considered as a next diagnostic test.

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K^+チャネル開口薬—基礎と臨床

4. イオンチャネル病とK^+チャネル開口薬

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分子遺伝学的研究の進歩により，一部の致死性不整脈疾患は心筋イオンチャネル機能に関係する遺伝子の変異によって発症することが判明し，「イオンチャネル病」という概念が生まれた．これには先天性または後天性QT延長症候群(LQTS)，Brugada症候群などが含まれる．先天性LQTSでは現在までに8つの遺伝子型が同定されているが，動脈灌流左室心筋切片を用いたLQTSモデルや単相性活動電位記録を用いた臨床研究により，K^+電流(I_{Ks}，I_{Kr})の機能低下によるLQT1とLQT2では，ATP感受性K^+(K_{ATP})チャネル開口薬のニコランジルの有効性が主に静注薬で示唆されている．一方，Brugada症候群ではNa^+チャネル遺伝子の*SCN5A*の異常が報告されているが，その病態には一過性外向き電流(I_{to})に関係する右室心外膜細胞活動電位の第1相notchが関与する．このため，K^+チャネル開口薬の使用や虚血時のATP感受性K^+電流($I_{K,ATP}$)増強は，表現型(ST上昇や心室細動)を増悪させたり，これを顕性化させる可能性がある(後天性Brugada症候群)．

(心電図，2006；26：20～27)

Keywords
- イオンチャネル
- 遺伝子
- QT延長症候群
- Brugada症候群
- K^+チャネル開口薬

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Ⅰ．はじめに

不整脈疾患のなかには家族性を認めるものがあり，その背景に以前から遺伝的素因の存在が示唆されていた．1995年に先天性QT延長症候群(LQTS)で最初のK^+およびNa^+チャネルの遺伝子変異が報告されて以来，いくつかの致死性不整脈疾患が，心筋イオンチャネル機能や細胞膜蛋白の調節に関係する遺伝子の変異によって発症することが判明し，

K^+ channel opening drugs : basic mechanisms and clinical application
K^+ channel opener in the ion channelopathy
Wataru Shimizu, Takeshi Aiba, Takashi Noda, Kazuhiro Satomi, Kazuhiro Suyama, Takashi Kurita, Naohiko Aihara, Shiro Kamakura

表1　先天性QT延長症候群の原因遺伝子とイオンチャネル機能

タイプ	遺伝子座	原因遺伝子	イオンチャネル
Romano-Ward症候群			
LQT1	11(11p15.5)	*KCNQ1*	I_{Ks}
LQT2	7(7q35-36)	*KCNH2*	I_{Kr}
LQT3	3(3p21-24)	*SCN5A*	I_{Na}
LQT4	4(4q25-27)	*Ankyrin-B*	Na-K ATPase、I_{Na-Ca}
LQT5	21(21q22.1-q22.2)	*KCNE1*	I_{Ks}
LQT6	21(21q22.1-q22.2)	*KCNE2*	I_{Kr}
LQT7	17(17q23)	*KCNJ2*	I_{K1}
LQT8	12(12p13.3)	*CACNA1C*	I_{Ca-L}
Jervell & Lange-Nielsen症候群			
JLN1	11(11p15.5)	*KCNQ1*(homozygous)	I_{Ks}
JLN2	21(21q22.1-q22.2)	*KCNE1*(homozygous)	I_{Ks}

「イオンチャネル病」という概念が生まれた[1](表1)．イオンチャネル病のなかでも，先天性LQTSでは，複数の異なる原因遺伝子が同定されており，遺伝子型と表現型(臨床病態)との関連が詳細に検討され，すでに遺伝子型特異的な治療が実践されつつある．K^+チャネル開口薬は，外向き電流を増強させることにより，理論的には活動電位持続時間(APD)やQT時間を短縮して，治療薬としての効果が期待されている．

一方，1998年に心筋Na^+チャネル遺伝子である*SCN5A*の変異がスペイン人家系で初めて報告されたBrugada症候群では，つい最近まで同定される原因遺伝子は*SCN5A*のみであり，先天性LQTSに比べ，表現型との関連の検討は十分に行われてはいない．しかし，実験的Brugada症候群による検討から，その分子細胞電気生理学的機序が明らかとなっており，K^+チャネル開口薬をはじめとするイオンチャネルを修飾する薬剤がその病態に及ぼす影響について示唆されている．

本稿では，イオンチャネル病のなかでも，先天性LQTSとBrugada症候群に焦点を絞り，K^+チャネル開口薬の抗不整脈性および催不整脈性について概説する．

Ⅱ．先天性QT延長症候群

先天性LQTSは，通常安静時からQT時間の延長を認め，多くの場合，運動や精神的ストレスなどによる交感神経緊張時にtorsade de pointes(TdP)と称される多形性心室頻拍が出現する．失神などの重篤な症状や心室細動(VF)に移行した場合には突然死の原因となる遺伝性疾患である[2),3)]．現在までに8つの遺伝子型が報告されているが[3)](表1)，いずれの遺伝子型でも，心室筋活動電位プラトー相における外向き電流が減少(loss of function)，または内向き電流が増強(gain of function)することによりAPDが延長し，QT時間の延長をきたす[3)]．

先天性LQTSの遺伝子診断率は現在のところ50～70%であり，遺伝子診断される患者における各遺伝子型の頻度は，LQT1が40%，LQT2が30～40%，LQT3が10%で，この3つの遺伝子型で90%以上を占める．このため，頻度の多いLQT1，LQT2，LQT3患者では，遺伝子型と表現型(臨床的特徴)との関連が詳細に検討されており，遺伝子型に基づいた患者の生活指導や，遺伝子型特異的な薬物治療がすでに実践されつつある．また，実験的先天性LQTSモデルによる成績から，より理論的な治療法の可能性が示唆されている．

1．実験的先天性QT延長症候群モデルを用いた遺伝子型別のK^+チャネル開口薬の有効性

動脈灌流左室心筋切片は，浮動性微小電極を用いて，心内膜細胞から心筋中層に存在するAPDの長いMid-myocardial(M)細胞，心外膜細胞あるいはプルキンエ細胞の活動電位と，貫壁性双極心電図を同時に記録することができ，心筋各層の活動電位勾配(transmural voltage gradient)が，どのように心電図波形に反映されるかを検討することができる実験モデルである．また，このモデルではTdPなどの頻脈性不整脈が誘発されるため，種々の抗不整脈薬のTdPに対する有効性を定量的に評価することも可能である．

この動脈灌流左室心筋切片を用いて，遅延整流

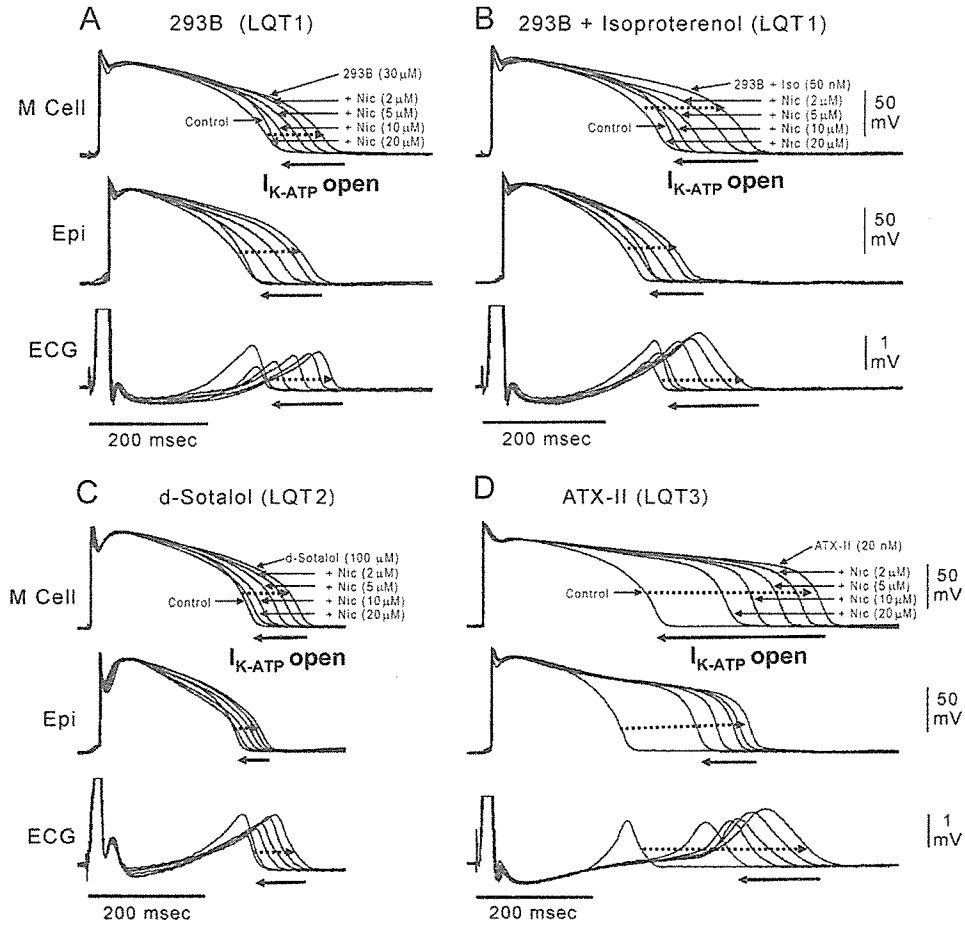

図1　動脈灌流左室心筋切片による実験的LQT1モデルにおけるK⁺チャネル開口薬（ニコランジル）の効果

上段から，M細胞，心外膜細胞（Epi）の活動電位と心電図（ECG）の同時記録を示し（basic cycle length = 2,000 msec），各薬剤容量時の活動電位を重ね合わせたものである．I_{Ks}遮断薬（chromanol 293B，30 μmol/L）を用いたLQT1モデルでは，β受容体刺激薬（イソプロテレノール，50 nmol/L）の非存在下（A），および存在下（B）のいずれにおいても，ニコランジル（Nic）は容量依存性（2～20 μmol/L）に活動電位持続時間（APD），QT時間，および貫壁性再分極時間のバラツキ（transmural dispersion of repolarization）をいずれも短縮し，20 μmol/Lのニコランジルはこれらをコントロールレベルまで短縮している．*D*-ソタロール（100 μmol/L）を用いたLQT2モデルでも，同様に20 μmol/Lのニコランジルはこれらをコントロールレベルまで短縮している（C）．一方，ATX-Ⅱ（20 nmol/L）を用いたLQT3モデルでは，20 μmol/Lのニコランジルはこれらを約50％程度しか減少させていない（D）．　〔文献6）より引用改変〕

K^+電流（I_K）の活性化の遅い成分（I_{Ks}）の遮断薬であるchromanol 293B（30 μmol/L）によりLQT1モデル，I_Kの活性化の速い成分（I_{Kr}）の遮断薬である*d*-ソタロール（100 μmol/L）によりLQT2モデル，late Na^+電流（I_{Na}）増強薬のATX-Ⅱ（20 nmol/L）によりLQT3モデルを作成した[4),5)]．LQT1モデルでは，β受容体刺激薬のイソプロテレノール（50 nmol/L）を併用し，さらにAPDが延長した状態を作成した[5)]．LQT1，LQT2，LQT3の3つの遺伝子型モデルで，ATP感受性K^+（K_{ATP}）チャネル開口薬であるニコランジルの容量依存性（2～20 μmol/L）の効果を検討したところ[6)]，LQT1，LQT2モデルでは，20

μmol/Lのニコランジルは QT時間，各細胞群のAPD，最長のM細胞APDと最短の心外膜細胞APDの差である貫壁性再分極時間のバラツキ(transmural dispersion of repolarization)をいずれもコントロールレベルまで短縮したが(図1A，B，C)，LQT3モデルでは，これらを50％程度しか減少させなかった(図1D)．また，これに一致してLQT1，LQT2モデルでは，20 μmol/Lのニコランジルは自然発生TdPまたは心外膜細胞からの単発期外刺激によって誘発されるTdPを完全に抑制したが，LQT3モデルでは，これらは完全に抑制されなかった．ただし，ニコランジルの有効血中濃度が，静注薬を用いた場合でも数μmol/Lであることを考慮に入れると，LQT3患者における効果は期待できず，LQT1とLQT2患者においてのみ，主に静注薬で補助的な抗不整脈作用が期待される程度と考えられる．

2．単相性活動電位記録を用いた臨床例におけるK^+チャネル開口薬の有効性

単相性活動電位(monophasic action potential：MAP)は，電気生理学的検査時にカテーテル電極を心内膜に押し付け，フィルター幅を広げることにより，心筋局所の活動電位波形を記録する方法である[7,8]．この方法を用いて，先天性LQTS患者のAPDに対するニコランジルの効果を臨床例で検討した[9]．交感神経刺激に対して最も感受性の高いLQT1患者で，心房ペーシングにより心拍数を一定とし(cycle length = 500 msec)，体表面12誘導心電図とともに右室および/または左室の2，3ヵ所で，MAPを同時記録した(図2)．コントロール時からQT時間の延長に一致して，90％MAP持続時間($MAPD_{90}$)の延長を認めたが，交感神経刺激薬のエピネフリン持続点滴(0.1 μg/kg/min)により，さらにこれらの延長を認め，症例によっては早期後脱分極(early afterdepolarization：EAD)様のhumpが記録された(図2)．また，心室筋各部位の最長と最短の$MAPD_{90}$の差である$MAPD_{90}$ dispersionもエピネフリン持続点滴により増大した(図2)．エピネフリンを持続点滴した状態でニコランジル(0.1 mg/kg)を静注したところ，$MAPD_{90}$の短縮とEADの消失，$MAPD_{90}$ dispersionの減少を認めた(図2)．さらに，β遮断薬のプロプラノロール(0.1 mg/kg)を静注したところ，これらの指標はコントロールレベルまで改善した(図2)．この結果は，K^+チャネル異常のLQT1では，交感神経刺激によりAPDやQT時間が著明に延長し，EADが出現するような状態では，K^+チャネル開口薬のニコランジルの静注薬が有効なことを示すものである．

以上の実験的および臨床的成績から，K^+チャネル開口薬(ニコランジル)は，Na^+チャネル異常のLQT3では有効性は期待できないが，K^+チャネル異常のLQT1やLQT2では有効性が期待できる．特に，LQT1では交感神経刺激による著明なQT時間の延長やTdPを認める際には，ニコランジルの静注薬によるQT時間の短縮やTdPの抑制効果が示唆された．

Ⅲ．Brugada症候群

Brugada症候群は，V_1からV_2 (V_3)誘導心電図におけるcoved型またはsaddle-back型のST上昇とVFを主徴とし，明らかな器質的異常を認めない疾患である[10,11]．

Brugada症候群では，1998年にLQT3型先天性LQTSの原因遺伝子でもある*SCN5A*の変異が初めて報告された[12]．つい最近，LQT2の原因遺伝子である*KCNH2*の変異を認めるBrugada症候群家系が報告されたが，それ以前に報告された唯一の原因遺伝子は*SCN5A*であること，また*SCN5A*の変異が同定されるのはBrugada症候群患者の18～30％にすぎないことから，遺伝子情報と臨床病態との関連の検討は十分になされてはいない[13]．

1．実験的Brugada症候群モデルによる分子細胞電気生理学的成因

Brugada症候群患者で報告されている*SCN5A*変異に共通する機能異常はfast Na^+電流の減少(loss of function)であり，これと特徴的なST上昇やVFなどの表現型との関連は，右室心筋細胞の貫壁性電位勾配で説明が可能なことが，動脈灌流右室心筋切片

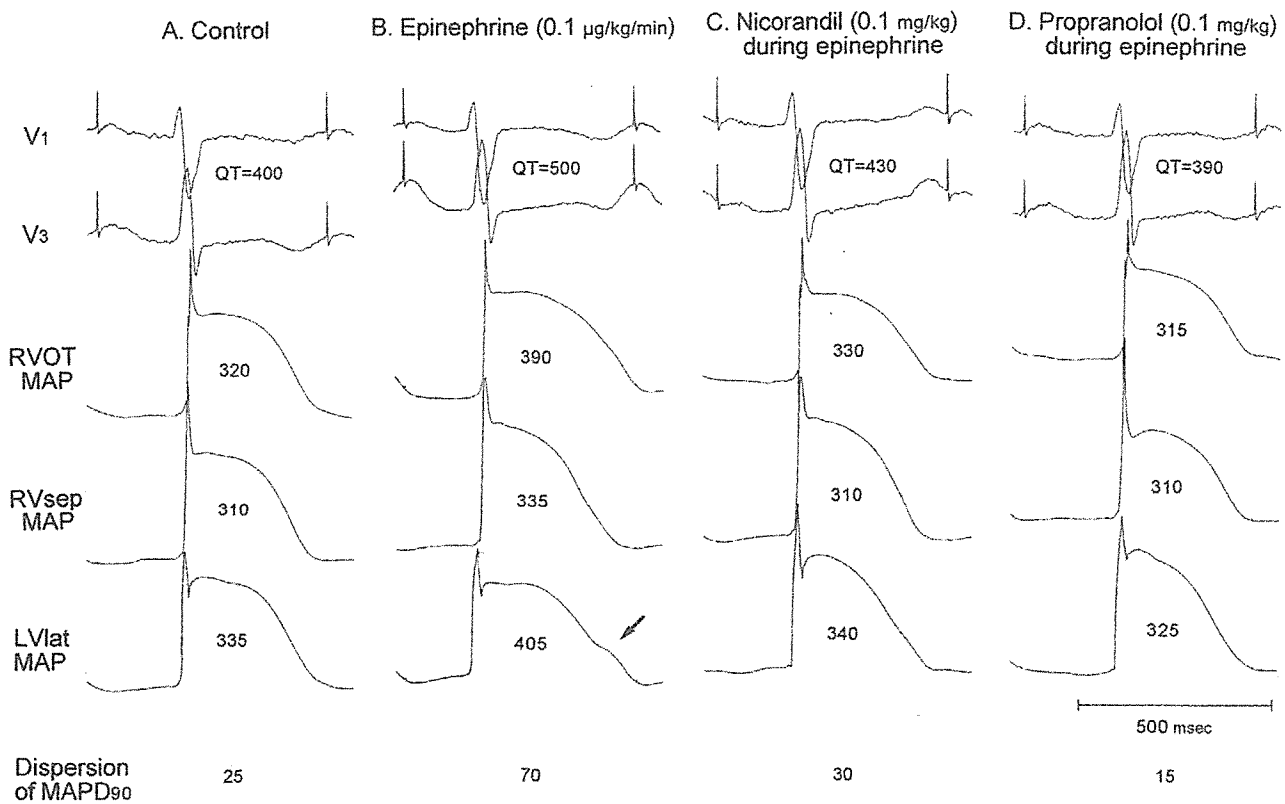

図2　LQT1型先天性QT延長症候群患者において，単相性活動電位(MAP)記録中にエピネフリン投与により出現した早期後脱分極(EAD)とMAP持続時間に対するK⁺チャネル開口薬(ニコランジル)とβ遮断薬(プロプラノロール)の効果

上段から体表面心電図のV_1, V_3誘導，右室流出路(RVOT)，右室中隔(RVsep)および左室側壁(LVlat)のMAPを示す．コントロール時にはEADは認めないが(A)，エピネフリン点滴静注(0.1 μg/kg/min)によりV_3誘導の増高したT波後方成分に一致してLVlat MAPにEADが記録され(矢印)，これに伴い同部位の90％MAP持続時間($MAPD_{90}$)は335 msecから405 msecへと著明に延長している(B)．ニコランジル(0.1 mg/kg)静注によりEADは消失し，各部位の$MAPD_{90}$およびQT時間は短縮し(C)，さらにプロプラノロール(0.1 mg/kg)静注によりコントロール時の状態に復している(D)．$MAPD_{90}$ dispersionはエピネフリン投与により25 msecから70 msecへ増大し，ニコランジルにより30 msecへ，プロプラノロールによりさらに15 msecへと縮小している．〔文献9)より引用〕

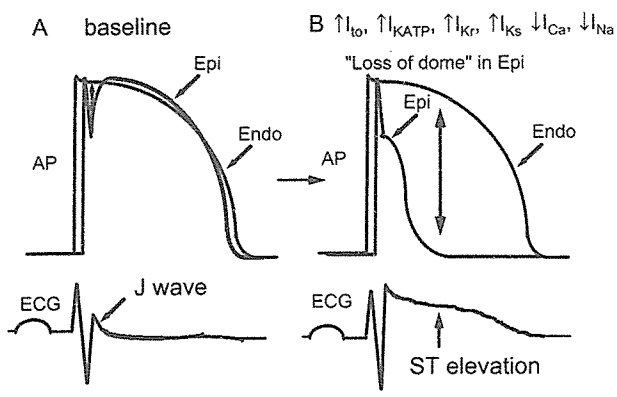

図3　Brugada症候群におけるST上昇の機序

本文参照．

を用いた実験的Brugada症候群モデルによる検討から明らかとなった[13), 14)]（図3）．すなわち，ST上昇またはJ波の増高には右室心外膜細胞における一過性外向き電流(I_{to})に関連した活動電位第1相notchが関係し，I_{to}や他の外向きK^+電流(I_{Kr}, I_{Ks}, ATP感受性K^+電流〔$I_{K.ATP}$〕など)が増加，または内向き電流($I_{Ca.L}$, fast I_{Na})が減少した場合に，心外膜細胞のnotchがさらに深くなりdomeが消失する(loss of dome)．心内膜細胞ではこのような変化は起こらないため，心外膜－心内膜細胞間で大きな電位勾配が生じ，J波およびこれに引き続くST部分が上昇する(図4)[13)]．

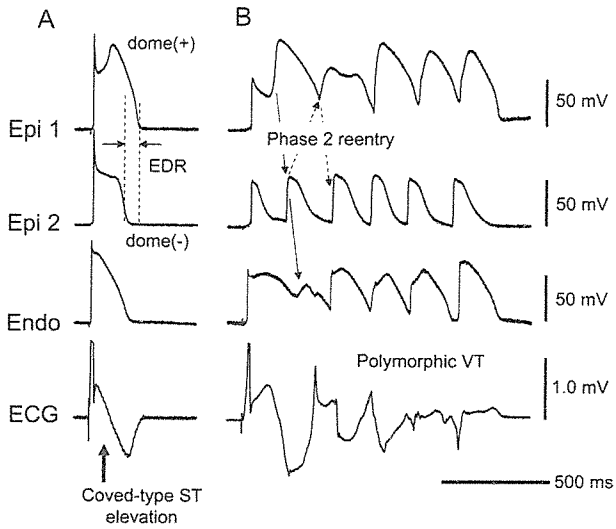

図4　動脈灌流右室心筋切片において$I_{Ca,L}$拮抗薬のテルフェナジンとfast I_{Na}遮断薬のピルジカイニドを用いて作成したBrugada症候群モデル

いずれも，近接する心外膜細胞2ヵ所(Epi 1，Epi 2)および心内膜細胞(Endo)の活動電位と心電図(ECG)の同時記録を示す(basic cycle length = 2,000 msec)．

A：Epi 1では深い活動電位第1相notchとdomeを認め，Epi 2ではdomeが消失しており，Endoとの電位勾配により，ECG上Brugada症候群に典型的なcoved型のST上昇を認める(矢印)．

B：Epi 1- Epi 2間での電位勾配によって，phase 2 reentryにより多形性心室頻拍が誘発されている(点線)．

〔文献13)より引用〕

VFの引き金となる心室期外収縮は，近接する心外膜細胞領域にdomeが消失する細胞とdomeが保たれる細胞を認める場合，両心外膜細胞間で再分極時間のバラツキが増大して発生するphase 2 reentryという一種のリフレクションが機序と考えられている(図4)[13]．さらに，最近の膜電位感受性色素を用いた高感度光マッピング法による検討から，VFが持続するためには，前述の再分極異常に加えて，軽度の脱分極(伝導)異常が必要なことが明らかとなってきた[15]．

2．Brugada症候群におけるK^+チャネル開口薬の催不整脈性

Brugada症候群の分子細胞電気生理学的成因から，ネットの外向き電流を増強させる薬剤は，活動電位第1相notchを増大しloss of domeを引き起こして，Brugada症候群の表現型を増悪させる可能性がある．この代表的な薬剤は，強力なfast I_{Na}遮断作用を有し，負荷試験としてBrugada症候群の診断にも用いられるIc群抗不整脈薬である[16]．一方，Ic群抗不整脈薬のほかにも，ネットの外向き電流を増強させる種々の薬剤により，Brugada様のST上昇やVFが引き起こされるとの報告もあり(表2)[11),17)]，後天性Brugada症候群あるいは後天性Brugada心電図という概念が生まれつつある[18]．

K^+チャネル開口薬によるBrugada症候群あるいはBrugada心電図の顕性化の報告は認めていない

表2　Brugada様ST上昇作用のある薬剤(後天性Brugada症候群)

1．抗不整脈薬
(1)Na^+チャネル遮断薬
　Ic群抗不整脈薬
　　フレカイニド，ピルジカイニド，プロパフェノン
　Ia群抗不整脈薬
　　アジマリン，プロカインアミド，ジソピラミド，シベンゾリン
(2)Ca^{2+}チャネル遮断薬
　　ベラパミル
(3)β遮断薬
　　プロプラノロールなど

2．抗狭心症薬
(1)Ca^{2+}チャネル遮断薬
　　ニフェジピン，ジルチアゼム
(2)亜硝酸薬
　　硝酸イソソルビド，ニトログリセリン
(3)K^+チャネル開口薬
　　ニコランジル

3．向精神薬
(1)三環系抗うつ薬
　　アミトリプチリン，ノルトリプチリン，desipramine，クロミプラミンなど
(2)四環系抗うつ薬
　　マプロチリンなど
(3)フェノチアジン誘導体
　　ペルフェナジンなど
(4)選択的セロトニン再取り込み阻害薬
　　fluoxetineなど

4．その他
(1)ヒスタミンH_1受容体拮抗薬
　　ジメンヒドリナートなど
(2)コカイン中毒
(3)リチウム

〔文献11)，17)より引用改変〕

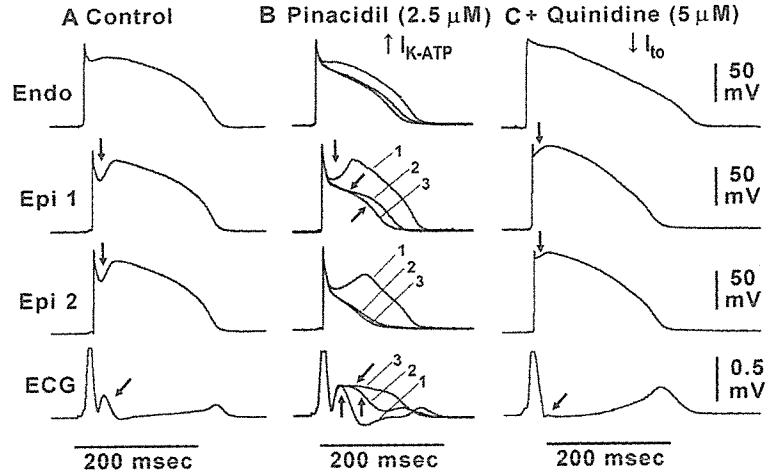

図5. 動脈灌流右室心筋切片によるBrugada症候群モデルにおけるK⁺チャネル開口薬(pinacidil)の影響とキニジンの効果

心内膜細胞(Endo)1ヵ所，心外膜細胞2ヵ所(Epi 1，Epi 2)の活動電位と心電図(ECG)の同時記録を示す(basic cycle length = 2,000 msec)．Pinacidil (2.5 μmol/L)灌流中の記録は，灌流開始後20 secごとの経時的な記録を重ね合わせたものである．コントロール時から，心外膜細胞でのみ深いnotchを認め，心内膜細胞との電位勾配によりECG上J波を認める(A)．Pinacidilにより，Epi 1およびEpi 2でnotchが深くなり，さらにdomeが消失して，ECG上はJ波が増高した後ST上昇を認めている(B)．一過性外向き電流(I_{to})遮断作用を有するキニジン(5 μmol/L)によりnotchが消失，domeが回復して，ECG上ST上昇は改善している(C)．〔文献14)より引用改変〕

が，動脈灌流右室心筋切片を用いた実験的Brugada症候群モデルでは，K⁺チャネル開口薬のpinacidilによりST上昇が増強することが報告されており(図5)[14]，特にBrugada症候群患者では，K⁺チャネル開口薬の使用にあたっては留意する必要がある．

Ⅳ．ま と め

先天性LQTSでは，いずれの遺伝子型でもネットの外向き電流が減少することによりAPDおよびQT時間が延長する．そのため，特にK⁺チャネル異常のLQT1およびLQT2では，著明なQT時間の延長時やTdP発作時に，主に静注薬でK⁺チャネル開口薬の有効性が期待される．一方，Brugada症候群では，逆にネットの外向き電流が増強することによりST上昇などの表現型が増悪することから，K⁺チャネル開口薬はBrugada症候群を増悪させたり，これを顕性化させる可能性がある(後天性Brugada症候群)．

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Editorial

局所活動電位持続時間の差異とST-T波の成因

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心電図上のST-T波は，QRS波の終わりからT波の終わりまでの部分をさし，QRS波直後または一部これに重複するJ波，これに引き続くST部分，およびT波から構成される．さらに，早期再分極相(J波とST初期)と後期再分極相(ST後期とT波)に分けることもできる．QRS波の成因が，例えば右脚ブロックや左脚ブロックのように，心室筋の脱分極(興奮伝導)の順序(パターン)により比較的理解しやすいのに対して，ST-T波の成因は，心室筋各部位の再分極過程の差異を反映するものであることは漠然と理解できても，それが実際にはどのようにST-T波に反映されているかは長らく不明であった．心室筋再分極相における電位勾配の形成には，心尖部と心基部，左室と右室，または左室前壁と後壁などの心室筋の空間的(spatial)な部位の違いによる活動電位波形の違いが関与する．

一方，1991年にSicouriとAntzelevitchにより，イヌ心室筋中層において活動電位持続時間(APD)の長いmid-myocardial(M)細胞の存在が報告されて以来，心外膜細胞からM細胞，さらに心内膜細胞にかけての貫壁性の活動電位勾配(transmural voltage gradient)が重要であることが明らかとなった．特に胸部誘導心電図で，右室自由壁の電位を反映するV_1，V_2誘導，左室自由壁の電位を反映するV_5，V_6誘導などの単極誘導心電図では，ST-T波の成因に貫壁性活動電位勾配が重要と考えられる．M細胞は，病理学的には心外膜細胞や心内膜細胞と区別することができないため，いまだにその存在を疑問視する意見もある．しかし，機能的(電気生理学的，薬理学的)には，徐脈時や種々の薬剤に対して選択的にAPDが延長し，早期後脱分極(EAD)などの異常自動能が誘発されやすい細胞群(M細胞)が存在することは，最近の報告でも証明されている．

早期再分極相のJ波は，活動電位レベルでは一過性外向きK^+電流(I_{to})による第1相notchの時相に一

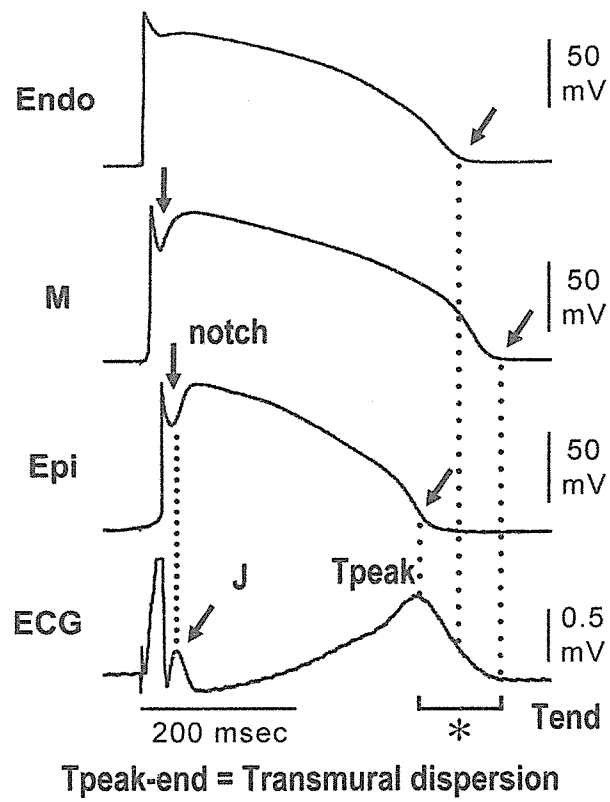

図　動脈灌流左室心筋切片を用いた貫壁性再分極時間とJ波，ST-T波の関係

心内膜(Endo)細胞，M細胞，心外膜(Epi)細胞の活動電位と心電図(ECG)の同時記録を示す(本文参照)．

致する(図)．第1相notchは，貫壁性のI_{to}の電流密度を反映して，心外膜細胞で最も大きく，M細胞では中等度であり，心内膜細胞ではほとんど認めない(図)．この貫壁性の第1相notch部分の電位勾配によりJ波が形成される(図)．古くからOsborn波として低体温患者に認める増大したJ波は，低体温によりI_{to}が増強し，心外膜細胞のnotchが増大することによると考えられる．特徴的なST上昇と心室細動を認めるBrugada症候群では，つい最近まで同定される原因遺伝子はNa^+チャネル遺伝子の*SCN5A*のみであったが，その病態には早期再分極相のI_{to}によるJ波が関与する．すなわち，活動電位第1相でI_{to}や他の外向きK^+電流が増加，または内向き電流が減少する場合に，心外膜細胞のみでnotchがさらに深くなり，心外膜－心内膜細胞間での貫壁性活動電位勾配が増大するためにJ波を含めたSTの初期成分が増高すると考えられている．

一方，後期再分極相のST-T波には，活動電位第2～3相(プラトー相)の貫壁性活動電位勾配が関与している(図)．正常T波の場合，心外膜細胞APDが最短で，心内膜下のM細胞APDが最長となり，心内膜細胞APDはM細胞と心外膜細胞の中間となる．陽性T波終末点は最長のM細胞の再分極点に，T波頂点は最短の心外膜細胞の再分極点に一致する(図)．このため，T波頂点からT波終末点までの時間(Tpeak-end)は，その誘導点が反映する心室筋領域の貫壁性再分極時間のバラツキ(transmural dispersion of repolarization：TDR)を反映すると考えられている(図，＊)．QT延長症候群(LQTS)は，後期再分極相の延長による疾患である．先天性LQTSでは8つの遺伝子型が報告されているが，いずれの遺伝子型においても，活動電位プラトー相における外向き電流が減少，または内向き電流が増強することによりAPDやQT時間が延長し，さらにEADが誘発され，TDRが増大することによりtorsade de pointes型の多形性心室頻拍が誘発されると考えられている．