4.4. Study limitations

In this retrospective study, some patients had suboptimal echocardiographic recordings for measurements of aortic diameters (at supraaortic ridge and ascending aorta level) and these measurements were not included in the analysis. Furthermore, although all study patients had color Doppler recordings, only 63% of all patients had pulsed Doppler recordings. Despite of the small number of patients, the difference in LV filling pattern between the 2 groups was very prominent and consistent.

Although transmitral flow velocity pattern provides a measure of diastolic filling, almost all of the indexes derived from the pattern are load dependent [19]. Again, note that in this study LV size, wall thickness, blood pressure, and the severity of aortic regurgitation and mitral regurgitation were comparable between the 2 patient groups in which pulsed Doppler examination was performed. Therefore, effects of loading conditions would be minor.

Since only 2 patients, both from the rapid progression group, received β-blocker therapy, effect of therapy could not be addressed in this study. To clarify the relationship between LV performance and progression of aortic root dilatation, a prospective study should be conducted with a larger number of patients.

4.5. Conclusions

Marfan patients at older age, with higher blood pressure, and with significant aortic regurgitation were at high risk of progression of aortic dilatation, with the most remarkable increase at the sinuses of Valsalva. LV systolic function appeared not to relate to the progression of aortic root dilatation. Prolonged deceleration time may relate to an increased risk for aortic complications.

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Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era

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Purpose This study was undertaken to assess the association between acute hyperglycemia and inhospital outcome after acute myocardial infarction (AMI) in the percutaneous coronary intervention (PCI) era. We also assessed outcome of patients with a history of diabetes mellitus in the PCI era.

Methods Between January 2001 and December 2001, 1253 patients were admitted to the hospitals within 48 hours after the onset of AMI. Plasma glucose was measured at hospital admission. Acute hyperglycemia was defined as plasma glucose of >11 mmol/L (198 mg/dL), regardless of the diabetic status. Primary PCI was performed in 898 (72%) patients.

Results The inhospital mortality rate was significantly higher in patients with acute hyperglycemia than in patients without (16% vs 6%, $P < .001$). However, there was no significant difference in mortality between diabetic and nondiabetic patients (8% vs 9%, $P = .54$). Acute hyperglycemia was associated with a higher inhospital mortality rate both in nondiabetic patients (24% vs 6%, $P < .001$) and in diabetic patients (10% vs 5%, $P = .039$). Acute hyperglycemia was associated with a higher incidence of no reflow during PCI (21% vs 12%, $P < .001$), but diabetes was not (14% vs 15%, $P = .71$).

Conclusion Acute hyperglycemia, but not diabetes, was a predictor for inhospital mortality after AMI in the PCI era. No reflow occurred more frequently during PCI in patients with acute hyperglycemia, suggesting that microvascular dysfunction might have contributed to adverse outcome of these patients. (Am Heart J 2005;150:814-820.)

An increase of plasma glucose concentration is often observed during early hours after the onset of acute myocardial infarction (AMI) not only in patients with diabetes mellitus but also in patients without diabetes mellitus.[1] It has been reported that both acute hyperglycemia and diabetes mellitus are independently associated with adverse outcomes after AMI in the prereperfusion era and in the thrombolytic era.[2-7] Primary percutaneous coronary intervention (PCI) has been shown to be more effective than thrombolytic therapy for the treatment of AMI.[8] Recent progress in treatment of AMI might have changed the association between acute hyperglycemia and outcome after AMI. This study was undertaken to assess the association between acute hyperglycemia and inhospital outcome after AMI in the contemporary PCI era. In addition, because acute hyperglycemia was often confused with chronic hyperglycemia, the association between diabetes mellitus and outcome after AMI in the PCI era was also investigated.

Despite the recent progress in PCI, it has been shown that coronary stent has no benefit in terms of reducing no-reflow phenomenon.[9] No-reflow phenomenon is associated with adverse outcome after AMI.[10,11] It has been reported that hyperglycemia impairs microvascular function and may cause no-reflow phenomenon.[12]

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**See Appendices.*

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Table I. Baseline characteristics of patients with and those without acute hyperglycemia

	Acute hyperglycemia		
	Present (n = 378)	Absent (n = 875)	P value
Age (y)	70 ± 12	67 ± 12	.007
Men	236 (62%)	648 (74%)	<.001
Hypertension	209 (55%)	489 (56%)	.85
Previous angina	115 (30%)	327 (37%)	.02
Previous infarction	59 (16%)	107 (12%)	.11
Diabetes mellitus	231 (61%)	166 (19%)	<.001
Time to admission (h)	5.7 ± 8.0	7.1 ± 9.3	.01
Killip classes 2 to 4	133 (35%)	143 (16%)	<.001
ST elevation	308 (81%)	745 (85%)	.11
Medication before infarction			
Aspirin	43 (11%)	88 (10%)	.49
ACE inhibitor	25 (7%)	54 (6%)	.77
ARB	10 (3%)	21 (2%)	.80
β-Blocker	18 (5%)	45 (5%)	.78
Ca channel blocker	89 (24%)	219 (25%)	.57
Nicorandil	13 (3%)	33 (4%)	.77
Statin	32 (8%)	54 (6%)	.15
Any of above medications	132 (35%)	283 (32%)	.37
Oral hypoglycemic drug	114 (30%)	58 (7%)	<.001
Insulin	49 (13%)	17 (2%)	<.001
Reperfusion therapy			
Thrombolysis	40 (11%)	64 (7%)	.06
Balloon angioplasty	43 (11%)	130 (15%)	.10
Stent	219 (58%)	506 (58%)	.97
Bypass surgery	9 (2%)	9 (1%)	.08
Neither	67 (18%)	168 (19%)	.54

Acute hyperglycemia was defined as plasma glucose of >11 mmol/L at admission, regardless of the diabetic status. *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

Table II. Baseline characteristics of patients with and those without diabetes mellitus

	Diabetes mellitus		
	Present (n = 397)	Absent (n = 856)	P value
Age (y)	67 ± 11	69 ± 13	.007
Men	273 (69%)	611 (71%)	.35
Hypertension	255 (64%)	443 (52%)	<.001
Previous angina	128 (32%)	314 (37%)	.12
Previous infarction	70 (18%)	96 (11%)	.002
Plasma glucose at admission (mmol/L)	13.2 ± 5.6	8.7 ± 3.4	<.001
Time to admission (h)	6.5 ± 8.9	6.8 ± 9.0	.70
Killip classes 2 to 4	102 (26%)	174 (20%)	.03
ST elevation	322 (81%)	731 (85%)	.06
Medication before infarction			
Aspirin	60 (15%)	71 (8%)	<.001
ACE inhibitor	37 (9%)	42 (5%)	.004
ARB	14 (4%)	17 (2%)	.11
β-Blocker	22 (6%)	41 (5%)	.57
Calcium-channel blocker	112 (28%)	196 (23%)	.04
Nicorandil	21 (5%)	25 (3%)	.04
Statin	45 (11%)	41 (5%)	<.001
Any of above medications	157 (40%)	258 (30%)	.001
Oral hypoglycemic drug	172 (43%)	0 (0%)	<.001
Insulin	66 (17%)	0 (0%)	<.001
Reperfusion therapy			
Thrombolysis	116 (29%)	216 (25%)	.14
Balloon angioplasty	59 (15%)	114 (13%)	.46
Stent	206 (52%)	519 (61%)	.004
Bypass surgery	9 (2%)	9 (1%)	.10
Neither	77 (19%)	158 (18%)	.69

Diabetes mellitus was defined as previous or current diagnosis of diabetes mellitus, regardless of the glycemic status at admission.

A second objective of this study was to ascertain whether acute hyperglycemia was associated with no-reflow phenomenon during PCI for AMI.

Methods

Patients

The JACSS is a retrospective observational multicenter study conducted at 35 medical institutions.[13] Between January 2001 and December 2001, 1640 consecutive patients who were admitted to the participating institutions within 48 hours after the onset of AMI were enrolled in the JACSS. Plasma glucose was measured at the time of hospital admission in 1253 (76%) patients, who constituted the current study group. Acute myocardial infarction was defined by a combination of 2 of the following 3 characteristics: chest pain consistent with ongoing myocardial ischemia persisting longer than 30 minutes, ischemic electrocardiographic changes, and peak creatine kinase value more than twice the normal upper limit.

Acute hyperglycemia was defined as plasma glucose of >11 mmol/L (198 mg/dL) at admission, regardless of the diabetic status. Patients were thought to have diabetes mellitus if they had previous or current diagnosis of diabetes mellitus, regardless of the glycemic status at admission. The study protocol was reviewed and approved by the ethical committee of each participating institution.

Coronary angiography and PCI

Percutaneous coronary intervention was performed as reperfusion therapy in 898 (72%) patients: coronary stent in 725 (58%) patients and conventional balloon angioplasty in 173 (14%) patients. The allocation of coronary angiography and reperfusion therapy was determined by physician's decision. The perfusion status of the infarct artery was assessed in accordance with the TIMI study classification.[14] Angiographic no-reflow was thought to be present if the perfusion of the infarct artery was TIMI-0 to TIMI-2 flow during PCI, despite the absence of stenosis of >50%, flow-limiting coronary dissection, or hypotension. Treatment of no-reflow, including intracoronary infusion of vasodilators, depended on the physician's decision.[15] Final TIMI flow grade was assessed on the final shot of the acute angiography.

End points

The primary end point was all-cause inhospital mortality. Other important clinical outcomes, including cardiac death, reinfarction, unstable angina, heart failure, and stroke, were also assessed during hospitalization. In patients who under-

Table III. The incidence of inhospital mortality and MACE

	Acute hyperglycemia			Diabetes mellitus		
	Present (n = 378)	Absent (n = 875)	P value	Present (n = 397)	Absent (n = 856)	P value
Death	60 (16%)	50 (6%)	<.001	32 (8%)	78 (9%)	.54 (ns)
MACE	76 (20%)	84 (10%)	<.001	56 (14%)	104 (12%)	.34 (ns)

MACE, Major adverse cardiac events including cardiac death, reinfarction, unstable angina, heart failure, and stroke; *ns*, not significant.

went PCI as reperfusion therapy, appearance of angiographic no-reflow during PCI was reported.

Data analysis

Statistical analysis was performed with the χ^2 test for categorical variables. The *t* test and analysis of variance were used for continuous variables. To assess the relationship between plasma glucose level and mortality, Cox proportional hazards regression model was used, and odds ratio (OR) and 95% CI were obtained. In this analysis, plasma glucose was used as a continuous variable. Multivariate analysis was performed adjusting diabetes mellitus, age, sex, hypertension, previous angina, previous infarction, time to admission, Killip class, ST elevation, use of cardiovascular medication before AMI, and PCI as reperfusion therapy. Differences were considered significant if the *P* value was <.05.

Results

Patient characteristics

Acute hyperglycemia was associated with older age, more women, more diabetes mellitus, more Killip class ≥2, less previous angina, and shorter time from the onset of AMI to admission (Table I). Diabetes mellitus was associated with younger age, more hypertension, more Killip class ≥2, more previous infarction, higher plasma glucose on admission, and less stent implantation (Table II).

There was no significant difference in medications before AMI between patients with acute hyperglycemia and patients without, except for more use of oral hypoglycemic drugs and insulin in patients with acute hyperglycemia. The use of cardiovascular medications was significantly more frequent in diabetic patients than in nondiabetic patients.

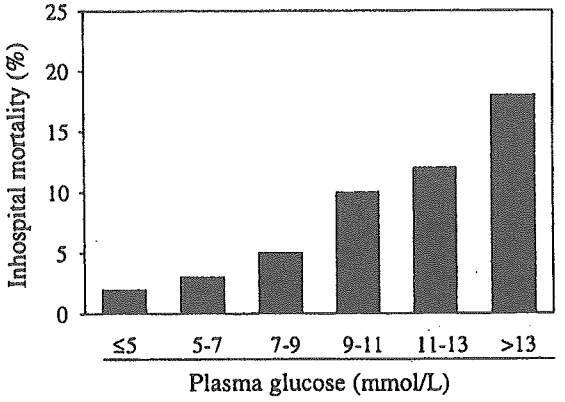
Hemoglobin A1c was measured during hospitalization in 561 (45%) patients. Hemoglobin A1c was 5.4% ± 0.5% in nondiabetic patients without acute hyperglycemia, 5.7% ± 0.8% in nondiabetic patients with acute hyperglycemia, 6.4% ± 1.1% in diabetic patients without acute hyperglycemia, and 8.0% ± 1.7% in diabetic patients with acute hyperglycemia ($P < .001$).

Inhospital outcomes

The inhospital mortality rate was significantly higher in patients with acute hyperglycemia than in patients without (Table III). Major adverse cardiovascular events, including cardiac death, reinfarction, unstable angina, heart failure and stroke, occurred more frequently in patients with acute hyperglycemia. The inhospital mortality increased as plasma glucose increased (Figure 1). An increase of 1 mmol/L (18 mg/dL) in plasma glucose was associated with an increase in mortality risk of 12% in univariate analysis (OR 1.12, 95% CI [1.08-1.16], $P < .001$) and 10% in multivariate analysis (OR 1.10, 95% CI [1.05-1.15], $P < .001$). On the contrary, there was no significant difference in the inhospital mortality rate and the major adverse cardiovascular events rate between diabetic and nondiabetic patients. Inhospital mortality of patients with acute hyperglycemia was twice as high as mortality of patients with diabetes mellitus (16% vs 8%). Acute hyperglycemia was associated with a higher inhospital mortality rate both in nondiabetic patients (24% vs 6%, $P < .001$) and in diabetic patients (10% vs 5%, $P = .039$).

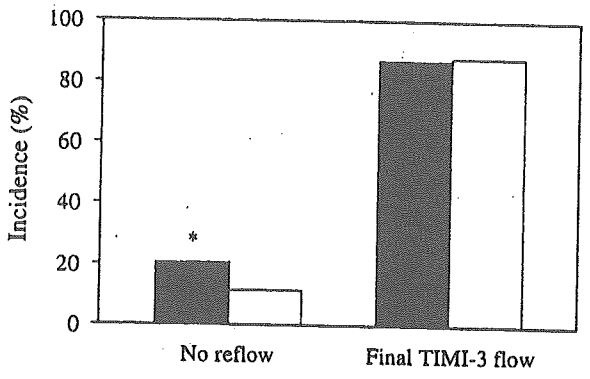
Peak creatine kinase was obtained in 1187 (94%) patients. Peak creatine kinase was significantly higher in

Figure 1



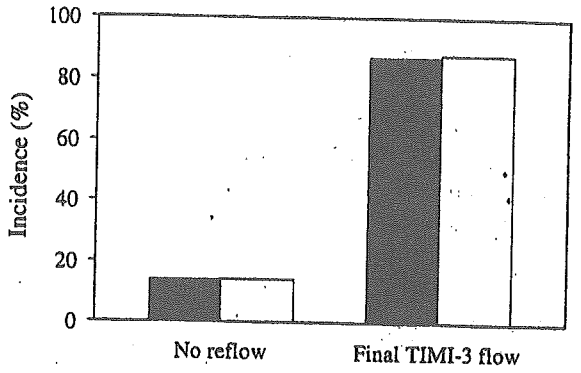
The inhospital mortality rate increased as plasma glucose increased (2% in patients with plasma glucose ≤5 mmol/L, 3% in patients with plasma glucose 5 to 7 mmol/L, 5% in patients with plasma glucose 7 to 9 mmol/L, 10% in patients with plasma glucose 9 to 11 mmol/L, 12% in patients with plasma glucose 11 to 13 mmol/L, and 18% in patients with plasma glucose >13 mmol/L; $P < .001$).

Figure 2



During coronary intervention, the incidence of angiographic no-reflow was more frequent in patients with acute hyperglycemia (black bars) than in patients without acute hyperglycemia (white bars). However, the incidence of final TIMI-3 was not different, *$P < .001$.

Figure 3



There was no significant difference in the incidence of angiographic no-reflow and final TIMI-3 flow between patients with diabetes mellitus (black bars) and patients without diabetes mellitus (white bars).

patients with acute hyperglycemia than in patients without (3176 ± 2945 vs 2698 ± 2557 IU/L, $P = .005$). However, there was no significant difference in peak creatine kinase between diabetic and nondiabetic patients (2695 ± 2580 vs 2905 ± 2730 IU/L, $P = .21$).

Angiographic no-reflow during PCI

See Figures 2 and 3. Among 898 patients who underwent PCI, angiographic no-reflow occurred in 128 (14%) patients during the procedure. Angiographic no-reflow was associated with a higher inhospital mortality rate (12% vs 5%, $P = .01$), a higher major adverse cardiovascular events rate (18% vs 9%, $P = .003$), and higher peak creatine kinase (4094 ± 3575 vs 2915 ± 2569 IU/L, $P < .001$). The incidence of angiographic no-reflow was significantly higher in patients with acute hyperglycemia than in patients without (21% vs 12%, $P < .001$) but was not different between diabetic and nondiabetic patients (14% vs 15%, $P = .71$). Acute hyperglycemia was associated with angiographic no-reflow both in nondiabetic patients (26% vs 12%, $P < .001$) and in diabetic patients (17% vs 9%, $P = .036$). The incidence of final TIMI-3 flow was not different regardless of the presence or absence of acute hyperglycemia (87% vs 88%, $P = .84$) or diabetes mellitus (87% vs 88%, $P = .73$).

Discussion

Although it has been demonstrated that increased plasma glucose at admission is associated with adverse outcome after AMI in the reperfusion era, most of these study patients were treated with thrombolysis, and there were few data on patients undergoing primary PCI.[6,7,16,17] Recently, Wahab et al[7] have reported that plasma glucose is an independent predictor of mortality after AMI in the thrombolytic era. However, only 34% of the study patients underwent thrombolytic therapy, and PCI was performed in <10% of the patients. JACSS is a contemporary multicenter study in which >70% of the patients underwent PCI as reperfusion therapy. We used the same definition of acute hyperglycemia as did Wahab et al, so that our result could be compared with previous findings. This study showed that acute hyperglycemia was associated with adverse inhospital outcome after AMI in the contemporary PCI era.

It remains controversial whether acute hyperglycemia predisposes to adverse outcome or is simply a consequence of large infarct size. A higher incidence of Killip class ≥2 suggests that acute hyperglycemia may reflect extensive myocardial damage. However, recent experimental studies have suggested that hyperglycemia per se exacerbates myocardial damage in AMI. Hyperglycemia increases interstitial fibrosis and myocyte apoptosis that exaggerate left ventricular remodeling.[18] Also, hyperglycemia abolishes the cardioprotective effect of ischemic preconditioning by closing K_{ATP} channels.[19,20] A recent clinical study reported that acute hyperglycemia was associated with impaired predischarge left ventricular ejection fraction in patients with AMI, independently of acute left ventricular ejection fraction.[21]

Another potential mechanism for the association between acute hyperglycemia and adverse outcome is microvascular dysfunction. Experimental studies have reported that hyperglycemia aggravates platelet-dependent thrombosis, increases circulating adhesion molecules that augment capillary leukocyte plugging, attenuates endothelium-dependent vasodilation, and reduces collateral blood flow by adversely affecting nitric oxide availability.[22-25] These changes impair microvascular function. Recently, Iwakura et al[12]

reported that hyperglycemia was associated with no-reflow phenomenon on myocardial contrast echocardiography in patients with angiographically successful reperfusion after PCI. No-reflow phenomenon is a strong predictor for adverse outcome after AMI.[10,11] We also showed that angiographic no-reflow occurred more frequently in patients with acute hyperglycemia, suggesting that impaired microvascular function might have contributed to adverse outcome after AMI in patients with acute hyperglycemia.

Interestingly, there was no significant difference in inhospital outcome between diabetic and nondiabetic patients. Previous studies have demonstrated that diabetes mellitus is associated with adverse outcome after thrombolysis for AMI.[26,27] In several studies that used noninvasive indices, reperfusion was achieved less frequently after thrombolysis in patients with diabetes mellitus than in patients without.[28] Angeja et al[29] reported that diabetes mellitus was associated with less complete ST-segment resolution after thrombolysis, even in patients with TIMI-3 flow. However, the incidence of complete ST-segment resolution was similar between diabetic and nondiabetic patients after PCI. More effective reperfusion by PCI, as compared with thrombolysis, may improve outcome of diabetic patients. Recent studies have reported that diabetes mellitus did not increase short-term mortality after AMI,[30-32] especially in non-insulin-requiring patients with diabetes.[33] Lower incidence of non-insulin-requiring patients with diabetes in this study (83% of diabetic patients) may also account for relatively favorable outcome of patients with diabetes mellitus. In addition, the use of cardiovascular medications before admission for the index episode of AMI was more frequent in diabetic patients than in nondiabetic patients. Pharmacological cardiovascular prevention might have offset the adverse effect of diabetes mellitus on short-term outcome after AMI.[30]

In this study, mortality was higher in nondiabetic patients with acute hyperglycemia than in diabetics with acute hyperglycemia. Although experimental studies have reported that diabetic hearts are tolerant to ischemia in some conditions,[33] it is unclear whether it may occur in human beings. One possible interpretation of this data is that unrecognized diabetes mellitus is a marker of adverse outcome in patients with AMI. However, the mean value of hemoglobin A1c of nondiabetic patients with acute hyperglycemia was significantly lower than that of diabetic patients with acute hyperglycemia ($P < .001$). Recent studies have reported that plasma glucose at admission is associated with increased mortality even after adjustment of hemoglobin A1c.[34] It is thus unlikely that the adverse outcome of nondiabetic patients with acute hyperglycemia is as a result of chronic hyperglycemia of undiagnosed diabetes mellitus.

This is a retrospective and observational study. However, it included all consecutive patients who were admitted to the participating institutions during the first year of the new millennium. Patients received contemporary management and >70% of the patients underwent PCI. Plasma glucose at admission was reported only in 76% of the patients enrolled in the JACSS. However, there was no significant difference in the incidence of diabetes mellitus (32% vs 28%, $P = .31$) and the inhospital mortality rate (9% vs 11%, $P = .34$) between patients with measurement of plasma glucose at admission and patients without. Because diabetes mellitus was defined as previous or current diagnosis of diabetes mellitus at the time of hospital admission, some of diabetic patients may not have been diagnosed as such. Oral glucose tolerance test was not usually performed during hospitalization, and it was not assessed how often nondiabetic patients with acute hyperglycemia at admission had newly diagnosed diabetes mellitus by the time of hospital discharge. We did not assess microvascular flow by using myocardial bluch grade or TIMI frame count, which might have provided additional information.

In conclusion, acute hyperglycemia, but not diabetes mellitus, was associated with inhospital mortality after AMI in the PCI era. Angiographic no-reflow occurred more frequently during PCI in patients with acute hyperglycemia, suggesting that microvascular dysfunction might have contributed to adverse outcome of these patients.

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Appendix A

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Review

The long QT syndrome: Therapeutic implications of a genetic diagnosis☆

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Abstract

The congenital long QT syndrome (LQTS) is a hereditary disorder characterized by a prolonged QT interval and a polymorphic ventricular tachycardia, known as Torsade de Pointes (TdP), leading to severe cardiac events such as syncope and/or sudden cardiac death. Molecular genetic studies have revealed a total of eight forms of congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21. Genotype–phenotype correlation in clinical and experimental studies has been investigated in detail in the LQT1, LQT2 and LQT3 syndromes which constitute more than 90% of genotyped patients with LQTS, enabling us to stratify risk and to effectively treat genotyped patients.

1. Introduction

Over the past decade molecular genetic research has established a link between a number of inherited lethal cardiac arrhythmias and mutations in genes encoding for ion channels or other membrane components. These inherited cardiac arrhythmias include the congenital and acquired long QT syndrome (LQTS) [1,2], the Brugada syndrome [3], progressive cardiac conduction defect (Lenegre disease) [4], catecholaminergic polymorphic ventricular tachycardia [5,6], arrhythmogenic right ventricular cardiomyopathy [7], familial atrial fibrillation [8], the familial sick sinus syndrome [9,10] and the short QT syndrome [11]. Genotype–phenotype correlations demonstrated in clinical and experimental studies have enabled us to stratify risk and to effectively treat patients with some of the inherited cardiac arrhythmia syndromes. The congenital LQTS is a Rosetta stone for studying the genetic basis of inherited cardiac arrhythmias, in that multiple genes encoding the different ion channels or membrane adaptor have been identified, and the genotype–phenotype correlation has been rigorously investigated.

The congenital form of LQTS is characterized by a prolonged QT interval in the electrocardiogram (ECG), and a polymorphic ventricular tachycardia known as Torsade de Pointes (TdP) [12–14]. Many patients with congenital LQTS suffer from severe cardiac events such as syncope and/or sudden cardiac death, most often during physical exercise or mental stress [15]. However, cardiac events occasionally occur at rest, during sleep, or under specific circumstances with arousal. Because familial cases of LQTS have long been recognized, inheritance was suggested before molecular screening became available. Since 1995, when the first two genes responsible for LQTS were identified [16,17], molecular genetic studies have revealed a total of eight forms of congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21 [18–21]. Mutations in KCNQ1 and KCNE1, the α and β subunits of the potassium channel gene, respectively, are responsible for defects (loss of function) in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying the LQT1 and LQT5 forms of LQTS [22,23]. Mutations in KCNH2 and

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KCNE2 cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for the LQT2 and LQT6 forms [16,24]. Mutations in SCN5A, the gene that encodes the α subunit of the sodium channel, result in an increase (gain of function) in the late sodium current (I_{Na}) responsible for LQT3 [17]. Mutations in KCNJ2 encoding for the inward rectifier potassium current (I_{K1}) were found to underlie Andersen–Tawil syndrome (LQT7), in which QT prolongation and ventricular arrhythmias are accompanied by periodic paralysis and dysmorphic features [19]. Recently, a mutation in Ankyrin-B, a member of a family of versatile membrane adapters, was reported to lead to the intracellular Ca^{2+} overload which underlies the LQT4 syndrome [20]. Most recently, a mutation in CACNA1C was reported to be responsible for the defect in the L-type calcium current ($I_{Ca\text{-}L}$) underlying the LQT8 form, an arrhythmia disorder associated with dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism [21]. At least some cases of sudden infant death syndrome (SIDS) are attributable to congenital LQTS [25], in which SCN5A mutations are reported [26,27]. In all genetic forms, decreases in outward potassium currents (I_{Ks}, I_{Kr}, I_{K1}) or increases in inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) prolong the action potential duration (APD), resulting in prolongation of the QT interval, a common phenotype in LQTS. However, responsible mutations can be identified among the 8 genes in only 50–70% of clinically affected LQTS probands, whereas the remaining 30–50% of probands cannot be genotyped. Of the 8 forms, the LQT1 and LQT2 syndromes are the two commonest genetic variants, and each accounts for approximately 40% of genotyped patients [18]. The LQT3 syndrome accounts for approximately 10% of genotyped patients [18]. Since the LQT1, LQT2 and LQT3 forms constitute more than 90% of genotyped patients with LQTS [18], the genotype–phenotype correlation has been investigated in detail in the LQT1, LQT2 and LQT3 syndromes.

2. Electrocardiographic characteristics

A greatly advanced knowledge of the cellular basis for the T wave in the ECG is attributed to experimental studies using arterially perfused canine ventricular wedge preparations, in which transmembrane action potentials from epicardial, mid-myocardial and endocardial cells are simultaneously recorded, together with a pseudo-ECG along the same axis [28–31]. The electrical currents which flow down voltage gradients on either side of the mid-myocardial region across the ventricular wall are believed to determine the morphology and duration of the T wave in the ECG, at least in the unipolar left precordial leads (V4–V6) which reflect the potentials of the left ventricular free wall. Under normal conditions, repolarization of the epicardial action potential occurs first, and coincides with the peak of the normal T wave, while repolarization of the longest action potential in the mid-myocardial layer coincides with the end of the T wave. Repolarization of the endocardial cells usually occurs between repolarization of the epicardial and the mid-myocardial cells. Because the action potential plateau consists of the sum of several ionic currents, differential modification of the ionic currents in each cell type by mutations in each LQTS gene is expected to result in a variety of QT interval and T wave morphologies.

Broad-based prolonged T waves are more commonly observed in the LQT1 syndrome, whereas low-amplitude T waves with a notched or bifurcated configuration are seen more frequently in the LQT2 syndrome [32]. LQT3 patients often show late-appearing T waves with a prolonged isoelectric ST-segment [32]. However, exceptions are present in all 3 genotypes [33], and the T wave pattern varies with time, even in the same patient with a specific mutation. The characteristic T wave morphology is reportedly revealed by exercise treadmill testing or catecholamine infusion in patients with LQT1 and LQT2 syndromes [34]. No specific T wave pattern has been suggested in the LQT5 and LQT6 syndromes. TU abnormalities such as biphasic T waves following long pauses like those found in the LQT2 syndrome are commonly observed in the LQT4 syndrome [20]. Enlarged U waves separated from the T wave, and frequent ventricular premature contractions are reported to be characteristic ECG features in the LQT7 syndrome [19].

Pharmacological LQTS models employing arterially perfused wedges have demonstrated that the differential time course of repolarization in the epicardial, mid-myocardial and endocardial cells as a result of mutations in each gene is responsible for the characteristic T wave morphologies in the LQT1, LQT2, LQT3 syndromes and probably in other genotypes [35–39].

3. Optimal management based on genotype–phenotype correlation

Previous clinical studies on genotype–phenotype correlation have reported differential triggers for cardiac events, clinical course and risk stratification between each genotype, especially in the LQT1, LQT2 and LQT3 syndromes.

3.1. Genotype-specific triggers for cardiac events

Clinical evidence has suggested genotype-specific triggers for cardiac events in patients with the LQT1, LQT2 and LQT3 syndromes [40–44]. Schwartz et al. analyzed data from the International LQTS Registry and reported that cardiac events most frequently occur during exercise (62%) but only rarely during sleep and rest (3%) in LQT1 patients [40,42]. Swimming is a common trigger in the LQT1 syndrome [41,43]. In contrast to the pattern shown in LQT1 patients, cardiac events principally occur during sleep and rest (39%), and exercise-related cardiac events are rare

(13%) in LQT3 patients [40]. In LQT2 patients, cardiac events occur equally during exercise (13%) or during sleep/rest (15%) [40]. More importantly, a sudden startle in the form of an auditory stimulus (a telephone, alarm clock, ambulance siren, etc.) is a specific trigger in the LQT2 syndrome [41,42]. Although the LQTS women are generally susceptible to cardiac events during postpartum periods, the LQT2 women have recently been reported to be most susceptible [44]. Exercise or mental stress often trigger ventricular arrhythmias in LQT4 patients [20]. In LQT7 patients, hypokalemia is often associated with frequent ventricular arrhythmias as well as periodic paralysis [19]. Information on genotype-specific triggers can enable physicians to take care of their LQTS patients more effectively. Exercise should be limited more strictly in LQT1 patients, in particular swimming or diving. LQT2 patients should be advised to avoid noises such as alarm clocks and telephones.

The experimental study by Priori et al. using guinea pig ventricular myocytes suggested for the first time that the genotype-specific triggers for cardiac events are a result of a differential response of ventricular repolarization to sympathetic stimulation between each genotype [45]. They demonstrated that the APD of cells pretreated with anthopleurin (LQT3 model) was shortened by β-adrenergic stimulation with isoproterenol, whereas the APD of cells exposed to dofetilide (LQT2 model) was even prolonged initially in response to isoproterenol. The increased sensitivity of LQT1 to sympathetic stimulation can be explained by the fact that genetically impaired I_{Ks} is unable to adequately shorten APD during sympathetic stimulation [46].

Experimental studies employing arterially perfused wedge preparations further advanced our knowledge on the mechanism of the genotype-specific triggers for cardiac events. The data suggest a genotype-specific response of the APD and the transmural dispersion of repolarization (TDR), defined as the difference between the maximum and the minimum APD across the ventricular wall, to isoproterenol in the LQT1, LQT2 and LQT3 models [35,38]. In the LQT1 model, isoproterenol prolongs the QT interval and the APD of the mid-myocardial cells, but abbreviates epicardial and endocardial APD, resulting in a persistent increase in the QT interval and the TDR, which may explain the greater sensitivity of LQT1 patients to sympathetic stimulation [38]. In the LQT2 model, isoproterenol initially prolongs and then abbreviates the QT interval and the mid-myocardial APD to the baseline level, whereas the epicardial and endocardial APD is always abbreviated, leading to a transient increase in the QT interval and the TDR, consistent with the nature of TdP, which is often observed following a startle [38]. In the LQT3 model, isoproterenol produces a persistent abbreviation of the QT interval and the APD of the all cell types, resulting in a persistent decrease of the QT interval and TDR, which may explain why cardiac events occur more frequently during sleep and rest when sympathetic tone is low in LQT3 patients [38].

3.2. Usefulness of provocative testing

The differential responses of ventricular repolarization to sympathetic stimulation between each genotype have also been investigated in clinical studies [34,47–52]. Clinical data using epinephrine infusion or treadmill exercise testing suggested that sympathetic stimulation produces genotype-specific responses of the QT interval and the Tpeak–Tend interval reflecting TDR in LQT1, LQT2 and LQT3 patients (Fig. 1A). Epinephrine remarkably prolongs the corrected QT (QTc) interval at peak effect when the heart rate is

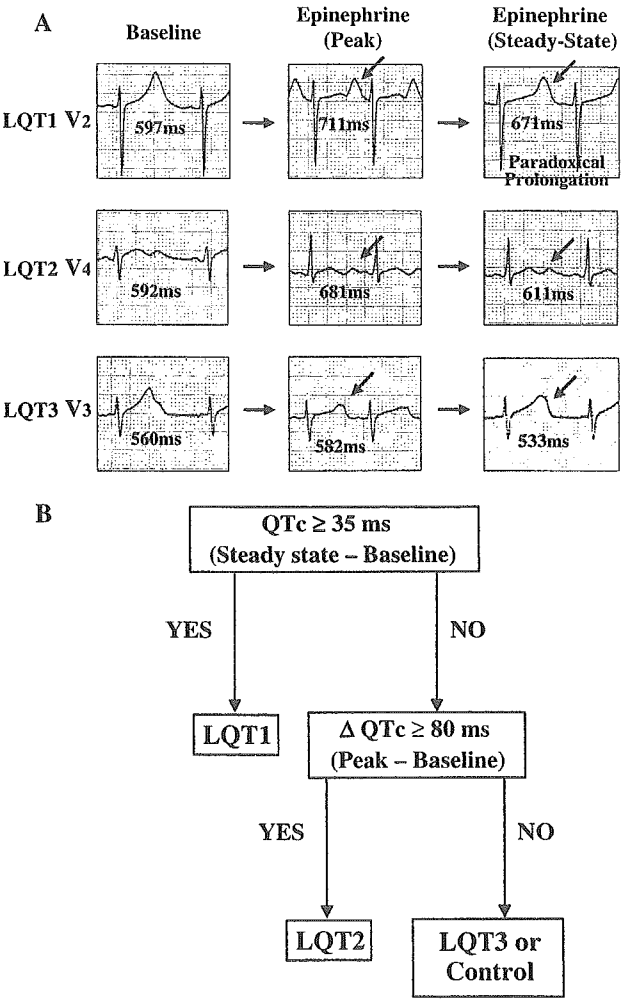

Fig. 1. Genotype-specific response of corrected QT (QTc) interval to epinephrine infusion (A) and genotype prediction by epinephrine infusion (B) in patients with LQT1, LQT2 and LQT3 syndromes. A: The QTc interval is markedly prolonged at the peak epinephrine effect (597 to 711 ms), and remains prolonged at the steady state epinephrine effect (671 ms—paradoxical prolongation of QT interval) in LQT1 patient (upper panels). In LQT2 patient, the QTc is also markedly prolonged at peak epinephrine effect (592 to 681 ms), but is abbreviated close to the baseline level at steady state epinephrine effect (611 ms) (middle panels). The QTc interval is slightly prolonged at peak epinephrine effect (560 to 582 ms) but much less than those in the LQT1 and LQT2 patients, and is shortened below the baseline level at steady state epinephrine effect (533 ms) in the LQT3 patient (lower panels). B: Schema illustrating a flow chart to predict genotype with the epinephrine test.

maximally increased (1–2 min after the start of epinephrine), and the QTc remains prolonged during steady-state epinephrine effect (3–5 min after the start of epinephrine) in LQT1 patients [48,51,52]. The QTc interval is also prolonged at peak epinephrine effect in LQT2 patients, but returns to close to the baseline levels at steady state epinephrine effect [48,52]. In contrast, the QTc is less prolonged at peak epinephrine effect in LQT3 patients than in LQT1 or LQT2 patients, and is abbreviated below the baseline levels at steady state epinephrine effect [48,52]. The response of the Tpeak–Tend interval approximately parallels that of the QT interval [47,50], supporting the cellular basis for genotype-specific triggers for cardiac events.

Epinephrine challenge is reported to establish an ECG diagnosis in silent mutation carriers of LQTS, especially the LQT1 genotype [51,52]. Epinephrine infusion is also useful to predict the genotype of the LQT1, LQT2 and LQT3 syndromes by the specific response of the QT interval (Fig. 1B) [52].

3.3. Genotype-specific clinical course

LQT1 and LQT2 patients show a higher frequency and cumulative probability of cardiac events than LQT3 patients [53]. However, the lethality of the cardiac events is higher in LQT3 patients. Male patients are generally younger than female patients at first cardiac events [54]. It is noteworthy that many first cardiac events occur before the age of 15 in male patients, particularly in LQT1 males, whereas female patients may experience first cardiac events after the age of 20 [54]. These data suggest that LQT1 males require stricter exercise restriction before the age of 15, but less restriction after age 15. More recently, risk stratification according to age, gender and QTc interval has been recommended [55]. For example, LQT1 and LQT2 patients and only LQT3 males who have a QTc interval of $\geq$500 ms are categorized as high risk groups—however, exceptions exist, and we must be very careful to advise each patient on a case-by-case basis.

4. Genotype-specific treatment based on clinical and experimental data

It has been empirically believed that β-blockers and strict exercise restriction are the most effective therapy for patients with congenital LQTS [56]. However, β-blockers are known not to be protective in all patients. A direct link between mutations in the ion channel genes and each genotype has made possible the advent of genotype-specific treatments for each LQTS genotype. In 1995, Schwartz and co-workers first reported the possibility of genotype-specific treatment. They demonstrated that sodium channel block with mexiletine or rapid heart rate is much more effective in abbreviating the QT interval in LQT3 patients than in LQT2 patients [57]. Preliminary clinical studies have since suggested the feasibility of genotype-specific therapy based on abbreviations of the QT interval by therapeutic agents or other interventions in each genotype [40,58]. However, the ability to abbreviate the QT interval by these interventions does not necessarily reflect their efficacy in reducing arrhythmic risk or sudden cardiac death. The experimental studies by pharmacological LQTS models using wedge preparations have provided a quantitative assessment of genotype-specific treatments for each LQTS genotype (Table 1) [28,35–39].

4.1. LQT1

4.1.1. β-Blockers

β-Blockers have long been the first choice of therapy in patients with congenital LQTS before molecular screening was available [56]. Clinical data from the International Registry of LQTS reported that β-blockers more frequently suppress an episode of syncope and sudden cardiac death in LQT1 patients (81%) than in LQT2 (59%) or LQT3 (50%) patients [40]. Priori et al. also studied the outcomes during β-blocker therapy for Italian LQTS patients, and found the same results [59]. Experimental data suggested that propranolol, a β-blocker, completely suppresses the effect of isoproterenol to persistently increase TDR and to induce TdP in the LQT1 model, supporting the genotype-specific efficacy of β-blockers in the LQT1 syndrome [35,38].

4.1.2. IB sodium channel blocker (mexiletine)

Although it is reported that mexiletine, a class IB sodium channel blocker which blocks late I_{Na}, abbreviates the QT interval dramatically in LQT3 patients [57], experimental data from wedge studies suggested that mexiletine reduces

Table 1
Genotype-specific therapy based on clinical and experimental data in long QT Syndrome

	LQT1 (LQT5)	LQT2 (LQT6)	LQT3
Sensitivity to sympathetic stimulation	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	– (↓ in TDR)
Torsade de Pointes Specific trigger	Exercise-related Swimming	Startle Telephone, Alarm clock, Postpartum periods	Sleep/Rest
Exercise restriction	+++++	+++	–
β-Blockers	+++++	+++	–
Potassium supply	++?	++++	++?
Class IB sodium channel blockers	+++	++++	+++++
Calcium channel blockers[a]	+++	+++	++?
Potassium channel openers[a]	++	++	–
Pacemaker	++	++	+++++
ICD	++++	++++	+++++

ICD, implantable cardioverter-defibrillator; TDR, transmural dispersion of repolarization. +++++ means most effective.
[a] Based only on experimental data.

TDR and suppresses the development of TdP equally in the LQT1, LQT2 and LQT3 models [28,35] This is mainly due to the intrinsically larger late I_{Na} in mid-myocardial cells than in epicardial or endocardial cells [60]. Therefore, mexiletine may at least warrant consideration as conjunctive therapy in addition to β-blockers in LQT1 patients.

4.1.3. Other pharmacological agents

We previously used monophasic action potential (MAP) recordings and reported that verapamil, an $I_{Ca\text{-}L}$ blocker, shortens the QT and MAP duration and suppresses epinephrine-induced early afterdepolarizations (EADs) in congenital LQTS patients, most of whom were diagnosed later as having the LQT1 or LQT2 syndrome [61]. Recent experimental studies also suggested the effectiveness of verapamil in decreasing the QT interval and TDR and abolishing EADs and TdP in a combination of congenital and acquired LQTS (LQT1+LQT2) [62]. Because verapamil is also a potent inhibitor of late I_{Na}, like many other calcium channel blockers, verapamil may also be suitable for conjunctive therapy.

Nicorandil, an $I_{K\text{-}ATP}$ opener, is clinically available in Japan and in some European countries. Clinical studies using MAP recordings demonstrated that intravenous administration of nicorandil reverses epinephrine-induced QT and MAP prolongation and suppresses epinephrine-induced EADs in LQT1 patients [63]. Our experimental study also suggested that relatively high concentrations (10–20 μmol/L) of nicorandil completely reverse the effects of chromanol 293B+isoproterenol and of D-sotalol to increase APD and TDR, and to induce TdP in the LQT1 and LQT2 models [39]. With regard to the therapeutic concentration of nicorandil, intravenous nicorandil may be of therapeutic value in suppressing repetitive episodes of TdP in the LQT1 and LQT2 patients, but not oral nicorandil.

It is noteworthy that prospective clinical data of the effectiveness of verapamil or nicorandil is lacking. Moreover, the series of LQTS treated with therapies other than β-blockers reported in the earlier studies showed unsatisfactory results [64]. Therefore, we will have to wait for prospective clinical trials to apply new strategies to LQTS patients.

4.1.4. Pacemakers

Previous MAP studies showed that atrial pacing not associated with sympathetic stimulation shortens the QT interval and MAP duration more significantly in LQTS patients (mostly LQT1 or LQT2) than in controls [65]. Moreover, experimental data from wedge studies showed that the APD-, QT- and TDR-rate relationships are much steeper in the LQT3 model than in the LQT1 or LQT2 models, but the relationships in the LQT1 and LQT2 models are still steeper than under control conditions [28,35], suggesting that pacemaker therapy may also be useful even in LQT1 patients, specifically those with bradycardia. The efficacy of combined use of β-blockers and long-term pacing therapy for patients with LQTS has been reported [66].

4.1.5. Left cardiac sympathetic denervation

The efficacy of left cardiac sympathetic denervation (LCSD) has been reported in LQTS patients, especially those who are refractory to β-blocker therapy [67,68]. Since LQT1 patients are most sensitive to sympathetic stimulation, LCSD is expected to be most effective in the LQT1 syndrome [68].

4.1.6. Implantable cardioverter-defibrillator

An implantable cardioverter-defibrillator (ICD) is indicated for LQTS patients who have suffered an aborted cardiac arrest and/or who have repetitive episodes of syncope in the presence of pharmacological and non-pharmacological therapy, regardless of genotype [69,70].

4.2. LQT2

4.2.1. β-Blockers

A β-blocker is the first choice of pharmacological therapy in LQT2 patients [40], however the recurrence rate is higher than that in LQT1 patients. Therefore, conjunctive pharmacological therapy with mexiletine and/or verapamil in addition to β-blockers is more frequently required in LQT2 patients.

4.2.2. Potassium supply

As the I_{Kr} defect is responsible for the LQT2 syndrome and I_{Kr} is sensitive to extracellular potassium level, serum potassium level is expected to play a key role in LQT2 patients. Experimental wedge studies suggested that an increase in extracellular potassium can limit the development of an arrhythmogenic substrate under long QT conditions, due principally to its action to increase I_{Kr} and I_{K1} and limit the potency of I_{Kr} blockers [29]. In clinical practice, exogenously administered potassium was reported to correct repolarization abnormalities in LQT2 patients with I_{Kr} defects [71]. Long-term oral potassium administration was recently shown to improve repolarization abnormalities in LQT2 patients [72]. Acute intravenous treatment with potassium is especially effective in suppressing TdP [73].

4.2.3. Pharmacological rescue

Albeit still at the experimental level, several agents, which block I_{Kr} current, were reported to rescue defective protein-trafficking of the KCNH2 mutations [74]. This pharmacological rescue may represent a new antiarrhythmic paradigm in the treatment of some trafficking-defective LQT2 mutations.

4.2.4. Pacemakers

Pause-dependent QT prolongation and a "short–long–short" initiating sequence of TdP are commonly observed in some patients with congenital as well as acquired LQTS [75]. Recently, pause-dependent TdP is reported to be more frequently recognized in LQT2 patients than in the other forms [76]. Therefore, constant pacing with pacemaker

therapy may be of therapeutic value in preventing TdP by suppressing pause in LQT2 patients.

4.2.5. Implantable cardioverter-defibrillator

The indication of the ICD is similar as that in the LQT1 syndrome.

4.3. LQT3

4.3.1. β-Blockers

Clinical data from the International LQTS Registry suggested that β-blockers are less effective in LQT3 patients than in LQT1 or LQT2 patients [40]. In experimental LQT3 models, sympathetic stimulation with isoproterenol persistently decreases TDR and suppresses TdP, and propranolol, a β-blocker, antagonizes the protective effects of isoproterenol [38], indicating that β-blockers are not protective or may even be harmful in LQT3 patients.

4.3.2. IB sodium channel blockers (mexiletine, flecainide)

Both preliminary clinical data and the experimental data employing wedge preparations suggested that mexiletine, a class IB sodium channel blocker, is more effective in abbreviating the QT interval in the LQT3 syndrome than in the LQT1 or LQT2 syndrome (Fig. 2B) [28,35,57]. These data encourage us to use mexiletine as a first line of therapy in LQT3 patients. However, an LQT3 patient, who was refractory to mexiletine, has recently reported [77]. At the moment, mexiletine should be used in the presence of β-blockers or with the backup of an ICD even in LQT3 patients until prospective clinical trials confirm the effectiveness of mexiletine.

Benhorin and co-workers reported the effectiveness of flecainide, a class IC sodium channel blocker, in abbreviating the QT interval in LQT3 patients with a specific mutation (D1790G) in SCN5A [78]. However, flecainide is reported to elicit a Brugada phenotype in some of LQT3 patients (Fig. 2C) [79]. Therefore, flecainide should not be used in LQT3 patients, except for those with this specific SCN5A mutation.

4.3.3. Pacemakers

Schwartz et al. indicated the specific efficacy of pacemaker therapy in LQT3 patients, because an increase of heart rate with exercise abbreviated the QT interval more effectively in LQT3 patients than in LQT2 patients [57]. The APD-, QT- and TDR-rate relationships in the experimental studies also supported the specific efficacy of pacing in the LQT3 syndrome, possibly due to slow kinetics of reactivation of late I_{Na} in this genotype [28,35].

4.3.4. Implantable cardioverter-defibrillator

As the lethality of the cardiac events is reported to be higher in LQT3 patients than in either LQT1 or LQT2 patients [53], an ICD implantation may be encouraged more aggressively in patients with LQT3 syndrome who experience an aborted cardiac arrest than patients with LQT1 or LQT2.

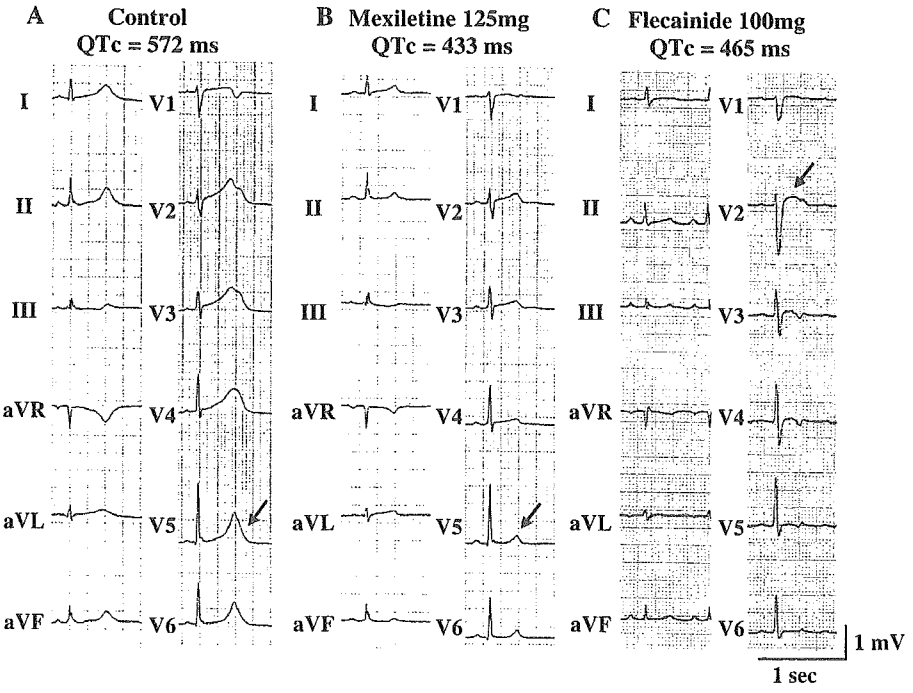

Fig. 2. Effects of sodium channel blockers, mexiletine and flecainide, in a patient with the LQT3 form of congenital long QT syndrome. A: The corrected QT (QTc) interval is prolonged (572 ms) under control conditions. B: Injection of mexiletine (125 mg), a class IB sodium channel blocker, normalizes the QTc to 433 ms. C: Injection of flecainide (100 mg), a class IC sodium channel blocker, also dramatically abbreviates the QTc to 465 ms, but unveils Brugada-like ST-segment elevation in lead V2.

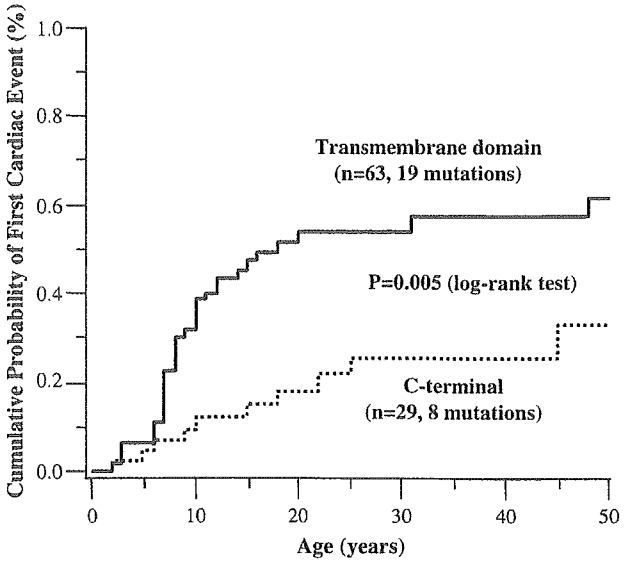

Fig. 3. Kaplan–Meier cumulative cardiac event curves from birth through to age 50 for patients with KCNQ1 mutations located in the transmembrane regions (N=66, 19 mutations) and the C-terminal regions (N=29, 8 mutations) in the LQT1 syndrome. The difference in the clinical course by mutation location was significant (log-rank, P=0.005), with a greater risk of first cardiac events in patients with transmembrane mutations than in those with C-terminal mutations.

4.4. LQT4 to LQT8

Genotype-specific management and treatment are unknown in the other forms, LQT4 to LQT8, because of the very small number of patients. β-Blockers are recommended in general, but an ICD should be considered to implant in patients with an aborted cardiac arrest and/or repetitive episodes of syncope refractory to β-blockers. Mutations in KCNE1 and KCNE2 in the LQT5 and LQT6 syndromes are responsible for defects of I_{Ks} and I_{Kr} respectively [22,23], therefore, therapy for LQT1 and LQT2 patients may be applied in LQT5 and LQT6 patients respectively.

4.5. Genotype-unknown LQTS

A β-blocker is the first line of therapy in patients with genotype-unknown LQTS, who account for 30–50% of clinically diagnosed LQTS patients. It is of importance to diagnose which form of the LQTS the patients are affected with on the basis of clinical test, such as epinephrine test. The genotype prediction by epinephrine test may help to stratify the treatment of patients, if the patients are not genotyped by the molecular screening.

5. Possibility of mutation site-specific management and therapy

To date, more than 300 distinct mutations involving the 8 LQTS genes have been reported, mainly in the LQT1, LQT2 and LQT3 genes. The structure of each cardiac ion channel or the correspondence between the mutation site

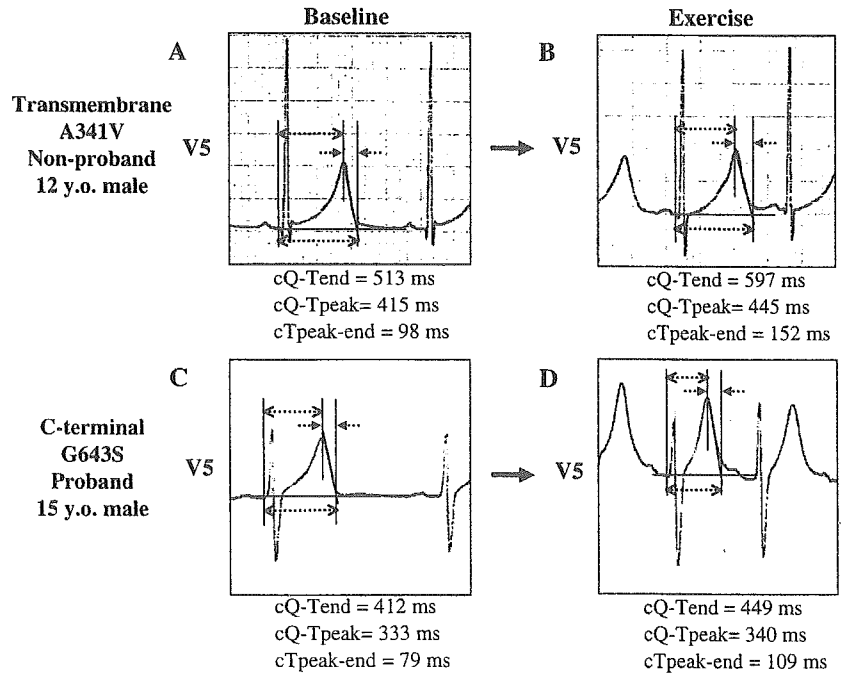

Fig. 4. ECG lead V5 before and after exercise treadmill testing in a LQT1 patient with the transmembrane mutation (A341V, non-proband, 12 years old, male) (A and B) and a LQT1 patient with a C-terminal mutation (G643S, proband, 15 years old, male) (C and D). The baseline corrected Q-Tend (cQ-Tend), Q-Tpeak (cQ-Tpeak) and Tpeak-end (cTpeak-end) intervals are greater in the patient with transmembrane mutation than in the patient with C-terminal mutation (A and C). The cQ-Tend and cTpeak-end are more markedly increased in the patient with transmembrane mutation than in the patient with C-terminal mutation (B and D).

and the channel function has been clearly disclosed. Therefore, mutation site-specific differences in severity of clinical phenotype or responses to therapy could be expected. In 2002, Moss and co-workers suggested that LQT2 patients with mutations in the pore region of the KCNH2 gene are at markedly increased risk of arrhythmia-related cardiac events compared with patients with non-pore mutations in the International LQTS Registry [80]. Regarding the LQT1 syndrome, Zareba et al. found no significant differences in the QTc interval or the risk of cardiac events based on the mutation location in the KCNQ1 gene [81]. Donger et al. had previously suggested that the specific missense mutation (R555C) located in the C-terminal region of the KCNQ1 gene was associated with a less severe phenotype than the mutations in the transmembrane regions [2]. We recently compared the arrhythmic risk and sensitivity to sympathetic stimulation with treadmill exercise testing between Japanese LQT1 patients with transmembrane mutations and those with C-terminal mutations in the KCNQ1 gene [82]. Our data suggested that patients with transmembrane mutations have a longer QTc and corrected Tpeak–Tend interval and more frequent LQTS-related cardiac events than those with C-terminal mutations (Fig. 3) [82]. Moreover, the QTc and corrected Tpeak–Tend were more prominently increased with exercise in patients with transmembrane mutations (Fig. 4) [82].

Our data in LQT1 as well as data by Moss et al. in LQT2 indicate the possibility of mutation site-specific management or treatment in each genotype. However, a tremendous clinical variability in a family with a specific mutation is often recognized. Therefore, a larger patient population is needed to make a definitive conclusion about the mutation site-specific differences in clinical phenotype.

6. Ethnicity and common polymorphisms

The discrepancy between our Japanese population and the population from the International Registry in mutation site-specific differences in clinical phenotype in the LQT1 syndrome may be in part attributable to ethnicity-specific common polymorphisms. Common polymorphisms in the ion channel gene is usually functionally silent — the functional phenotype associated with polymorphism channels is usually indistinguishable from the functional phenotype associated with wild-type channels. However, Splawski et al. suggested that a predominantly Negroid-specific common polymorphism, S1103Y in the SCN5A gene, is associated with arrhythmia risk [83], supporting the concept that common genetic determinants may mediate arrhythmia susceptibility. An Asian-specific common polymorphism, G643S in the KCNQ1 gene, has been shown to have a subtle functional LQTS-phenotype in vitro [84]. The prevalence of G643S is reported to be approximately 11% in the Japanese population, and 3 of the 15 patients with G643S for our Japanese cohort were brought to medical attention as an acquired form of LQTS associated with class IA antiarrhythmic agent and/or bradycardia (unpublished data). These data suggest that ethnicity-specific common polymorphisms can mediate genetic susceptibility for arrhythmia risk as well as modify clinical phenotype caused by a responsible mutation in the LQTS gene. Further systematic and comprehensive study on common polymorphisms is required to further advance the management and treatment of patients with LQTS.

7. Summary

Recent advances in molecular genetic studies have identified a total of eight forms of congenital LQTS caused by mutations in genes of the ion channels or membrane adapter. The direct link between mutations in the ion channel or membrane adapter genes and each LQTS genotype by genotype–phenotype correlation has made possible the advent of genotype-specific management and treatment for each LQTS genotype. Further prospective and comprehensive study on genotype– or mutation–phenotype correlation is needed to further advance the effective management and treatment of patients with congenital LQTS.

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Mechanisms of Disease: current understanding and future challenges in Brugada syndrome

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SUMMARY

Brugada syndrome is a clinical entity characterized by ST-segment elevation in the right precordial leads (V1–V3) and an episode of ventricular fibrillation in the absence of structural heart disease. Data regarding genotype–phenotype relationships are limited, since *SCN5A*, the gene encoding the α subunit of the sodium channel, is as yet the only gene linked to Brugada syndrome. Studies of *SCN5A* mutations responsible for the Brugada phenotype have shown the presence of functional defects in the sodium-channel current. Experimental studies employing arterially perfused right-ventricular wedge preparations have elucidated cellular mechanisms for this phenotype. Data indicate that an accentuated action-potential notch, mediated by a prominent transient outward current and loss of the action-potential dome in the epicardium (but not in the endocardium) of the right ventricle give rise to a transmural voltage gradient, resulting in ST-segment elevation and the induction of ventricular fibrillation. On the basis of cellular mechanisms, it might be possible to normalize the Brugada phenotype by use of therapeutic agents or interventions that decrease net outward currents by decreasing the transient outward current or outward potassium currents, or increasing the L-type inward calcium current or fast sodium current. Interventions that increase net outward currents through raising the transient outward current or outward potassium currents or decreasing the L-type inward calcium current or fast sodium current might aggravate or unmask the Brugada phenotype, resulting in an acquired form of this syndrome. In this review, we discuss future challenges relating to risk stratification, genetic heterogeneity, sex and ethnic differences in Brugada syndrome.

KEYWORDS Brugada syndrome, genotype, phenotype, ST segment, ventricular fibrillation

REVIEW CRITERIA

Articles were identified by searching the MEDLINE and PubMed databases, using the search keywords "Brugada syndrome", "mechanism", "therapy", "genotype" and "phenotype", alone or in different combinations. All articles were full-text, English-language papers. We also did a limited manual search of the references listed in these papers and in other papers in our files. Abstracts from the 2004 meeting of the American Heart Association were also searched using the terms listed.

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INTRODUCTION

Since the first description by Pedro and Josep Brugada[1] of eight patients with a history of aborted sudden cardiac death caused by ventricular fibrillation (VF) as a distinct clinical entity, numerous reports from around the world have demonstrated the clinical, electrocardiographic, electrophysiologic, cellular, ionic, genetic and molecular features of Brugada syndrome.[2–11] This syndrome is characterized by ST-segment elevation in the right precordial leads (V1–V3) and episodes of VF in the absence of structural heart disease.

PHENOTYPIC CHARACTERISTICS AND DIAGNOSTIC CRITERIA

Brugada syndrome usually manifests during adulthood, with a mean age of sudden death of 41 years (SD 15 years). More than 80% of patients affected with Brugada syndrome are men. The prevalence of male patients is highest in Asian countries, including Thailand and Japan.[12–14] The majority of VF episodes are documented as a form of sudden unexplained nocturnal death, syncope or agonal respiration during sleep at night. Two specific types of ST-segment elevation, coved and saddleback, are recognized in patients with the Brugada syndrome. Although the magnitude and morphology of ST-segment elevation alters with time,[15] the coved type is reportedly associated with a higher incidence of VF and sudden cardiac death.[7–11,16] Therefore, type 1 ST-segment elevation, which is defined as a coved ST-segment elevation of at least 0.2 mV (2 mm), with or without a terminal negative T wave, is required to diagnose Brugada syndrome.[8,11] Brugada syndrome is differentially diagnosed when a type 1 ST-segment elevation is observed in more than one of the V1–V3 leads, in the presence or absence of sodium-channel blocker, and is associated with more than one of certain features: documented VF, polymorphic ventricular tachycardia (PVT), a family history of sudden cardiac death (<45 years old), coved type electrocardiograms in family members,

inducibility of VF with programmed electrical stimulation, syncope or nocturnal agonal respiration.[8] Sodium-channel blockers, including flecainide, ajmaline and pilsicainide, amplify or unmask ST-segment elevation, and are used as a diagnostic tool in latent Brugada syndrome with transient or no spontaneous ST-segment elevation.[17,18] Shift of the right precordial leads (V1–V3) to the 3rd and 2nd intercostal spaces can increase the sensitivity of electrocardiography for detecting the Brugada phenotype in some patients.[11,19] During electrophysiologic study, VF or sustained PVT is induced in 50–70% of Brugada patients.[7,9,10,20,21] A family history of unexplained sudden death is present in 20–30% of Brugada patients.[7,20,21]

GENOTYPE–PHENOTYPE RELATIONSHIPS

In the past decade, significant advances have been made in molecular genetics that have established a link between a number of inherited cardiac arrhythmias, including Brugada syndrome, and mutations in genes encoding ion channels or other membrane components. The first mutation linked to Brugada syndrome was identified by Chen and co-workers[22] in *SCN5A*, the gene encoding the α subunit of the sodium channel. A second locus on chromosome 3, close to but distinct from the *SCN5A* locus, has also been linked to the Brugada syndrome in a large pedigree,[23] but the specific gene or genes affected have not yet been identified. At present, *SCN5A* mutations account for only 18–30% of patients diagnosed as having Brugada syndrome. *SCN5A* is the only gene linked to the Brugada syndrome so far, and data on genotype–phenotype relationships in clinical studies are, therefore, limited. Smits and co-workers[24] observed significantly longer conduction parameters (including PQ and HV intervals) in Brugada patients with *SCN5A* mutations than in those without *SCN5A* mutations. Although knowledge of a specific mutation in the *SCN5A* gene might not provide guidance on prognosis or risk stratification in Brugada syndrome, identification of these mutations might help to establish a clinical diagnosis. In addition, detection of *SCN5A* mutations might enable affected relatives who are at risk of developing Brugada syndrome to be identified, and advance our knowledge of genotype–phenotype relationships.

GENETIC AND FUNCTIONAL CHARACTERISTICS OF *SCN5A* MUTATIONS

Over 80 mutations in the *SCN5A* gene have been linked to Brugada syndrome in the past

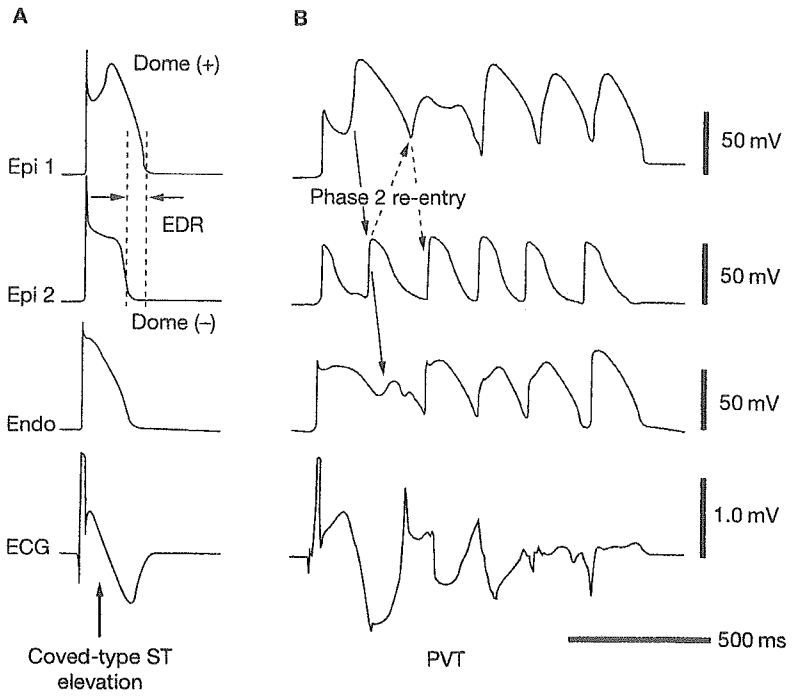

Figure 1 Coved-type ST-segment elevation and subsequent nonsustained polymorphic ventricular tachycardia caused by premature beats induced by phase 2 re-entry in a Brugada model, employing an arterially perfused canine right-ventricular wedge preparation. Transmembrane action potentials were simultaneously recorded from two epicardial sites and one endocardial site together with a transmural electrocardiogram (basic cycle length 2000 ms). (**A**) Combined administration of 5 μM/l terfenadine and 5 μM/l pilsicainide causes heterogeneous loss of the action-potential dome in the epicardium (restored dome in epicardial site 1, loss of dome in epicardial site 2), giving rise to coved-type ST-segment elevation and increasing epicardial dispersion of repolarization. (**B**) Electrotonic propagation from the site where the dome is restored (epicardial site 1) to the site where it is lost (epicardial site 2) results in development of a premature beat induced by phase 2 re-entry, triggering spontaneous polymorphic ventricular tachycardia. Dome (+), restored dome; dome (–), loss of dome; ECG, electrocardiogram; EDR, epicardial dispersion of repolarization; Endo, endocardial; Epi, epicardial; PVT, polymorphic ventricular tachycardia.

4 years.[7,25] Approximately two dozen of the mutations have been studied in expression systems, and have been shown to result in loss of function of the sodium-channel current (I_{Na}) by several mechanisms.[14,22,26–31] The following examples are among the functional effects that have been identified: lack of expression of the sodium channel; a shift in the voltage-dependence and time-dependence of I_{Na} activation, inactivation or reactivation; entry of the sodium channel into an intermediate state of inactivation from which it recovers slowly; accelerated inactivation of the sodium channel; or a trafficking defect. Interestingly, some of the gating effects are reported to result in a cardiac conduction defect rather than the Brugada phenotype.[32]