Effects of Glucose-Induced Insulin Secretion on Ventricular Repolarization in Patients With Congenital Long QT Syndrome

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To assess the role of insulin in ventricular repolarization in patients with congenital long QT syndrome (LQTS), an oral glucose tolerance (OGT) test was performed in 11 patients with LQTS and in 11 control cases without QT prolongation. Plasma glucose, potassium level and the immunoreactive insulin concentration (IRI) were measured, and the QT interval and T wave morphology on 12-lead ECG were analyzed during fasting and after glucose load. The LQTS group had a higher incidence of changes in T wave morphology, such as biphasic, bifid or notched T wave, after glucose load than the control group (11 of 11 patients [100%] vs 0 of 11 [0%]; $p < 0.00001$). The T wave changes returned to baseline at 180 min after glucose load in 7 patients. The maximal QT interval and QT dispersion increased significantly and returned to baseline level in response to IRI after glucose load in LQTS, whereas the QT interval was unaffected in the control group. After glucose load, ventricular arrhythmias and T wave alternans were observed in 3 and 1 patients with LQTS, respectively, but none in the control group. The findings suggest that glucose-induced insulin secretion plays a role in inducing abnormalities and inhomogeneity of ventricular repolarization in patients with LQTS. (Circ J 2002; 66: 35–40)

Key Words: Insulin; Long QT syndrome; QT dispersion; Ventricular arrhythmia; Ventricular repolarization

Insulin modulate ion transport mechanisms in cardiac and skeletal muscles, but has little influence on membrane potential other than hyperpolarization of the resting potential! A recent report suggested that insulin stimulates the L-type calcium current in isolated rat ventricular myocytes in a dose-dependent manner² and we recently reported that QT dispersion was associated with an increased plasma insulin level during an oral glucose tolerance (OGT) test in healthy volunteers.³ However, it is not known whether glucose-induced insulin secretion plays a functional role in abnormal ventricular repolarization in the human heart.

Congenital long QT syndrome (LQTS) caused by mutation of the cardiac potassium- and sodium-channel genes and their associated subunits has distinct ECG abnormalities of ventricular repolarization. The abnormal ST-T wave forms are variously affected by changes in physiological factors including serum electrolyte and catecholamine levels, which may underlie different phenotypes and time-dependent fluctuations of the ST-T changes in these patients.^{4–13} However, there has not been an exploration of

the effects of plasma insulin level after food intake or glucose load on ventricular repolarization in patients with congenital LQTS. We hypothesized that insulin might exert dose-dependent effects on ventricular repolarization in the human heart and that patients with congenital LQTS would be more sensitive to the insulin action than age-matched control healthy subjects with a normal QT interval. The present study was designed to investigate this hypothesis.

Methods

Study Patients

The study included 11 patients with congenital LQTS (4 men, 7 women; mean age, 25 ± 9 years, range 12–44) and 11 healthy age-matched volunteers with normal QT interval as the control group (5 men, 6 women; mean age, 27 ± 8 years, range 17–44). All 11 patients with congenital LQTS had a documented QTc interval (corrected QT interval with a modification of Bazett's formula¹⁴) greater than 480 ms (498 ± 40 ms) on 12-lead ECG before receiving medication. Ten patients had a history of stress-induced syncope, and one had a history of cardiac arrest. Torsades de pointes was documented in 8 patients: it was familial in 7 and sporadic in 4 patients.

Three patients with congenital LQTS were taking propranolol, one was taking propranolol and mexiletine, and 7 were not receiving any medication at the time of OGT test. The control group had a mean QT interval of 401 ± 27 ms. Both groups had normal results on physical examination and no overt diabetes mellitus, renal disease or endocrine disorders. Excluded were subjects with a systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 85 mmHg, total cholesterol greater than 12.2

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Table 1 Clinical Characteristics of Patients With Long QT Syndrome

Patient no.	Age (years) /sex	Symptoms		Family history	Diabetes mellitus	Medication
		Syncope	Tdp			
1	12/F	+	+	+	—	—
2	35/F	+	+	+	—	Propranolol
3	26/F	+	+	—	—	Propranolol
4	20/M	+	—	+	—	—
5	20/M	+	+	+	—	Propranolol Mexiletine
6	21/F	+	—	—	—	—
7	15/F	+	—	+	—	—
8	28/F	+	+	—	—	Propranolol
9	22/M	+	+	+	—	—
10	44/F	+	+	+	—	—
11	33/M	+	+	—	—	—

Tdp, torsade de pointes.

Table 2 Results of the Oral Glucose Tolerance Test

	Long QT syndrome (n=11)	Control group (n=11)	p value
Potassium level (mmol/L)			
Fasting	3.9±0.3	4±0.2	NS
30 min	4.0±0.3	4.0±0.3	NS
60 min	3.9±0.3	3.9±0.3	NS
120 min	3.9±0.2	3.9±0.3	NS
180 min	4±0.2	4±0.2	NS
Plasma glucose (mmol/L)			
Fasting	4.9±0.4	5.1±0.5	NS
30 min	7.9±1.9**	8.4±1.1**	NS
60 min	8.2±2.7**	9.1±1.6**	NS
120 min	7.0±1.5**	7.4±1.0**	NS
180 min	5.3±1.0	5.6±1.3	NS
IRI (pmol/L)			
Fasting	42±30	48±30	NS
30 min	384±462*	312±198**	NS
60 min	306±228**	366±174**	NS
120 min	246±132**	312±138**	NS
180 min	90±60	150±120*	NS

* $p<0.05$ vs Fasting, ** $p<0.01$ vs Fasting. IRI, plasma immunoreactive insulin concentration.

mmol/L (220 mg/dl), triglyceride greater than 8.3 mmol/L (150 mg/dl), a high-density lipoprotein cholesterol less than 2.2 mmol/L (40 mg/dl) or a body mass index greater than 25 kg/m². The clinical characteristics of the patients with congenital LQTS are presented in Table 1.

The study protocol was approved by the Ethics Committee of the institution and written informed consent was obtained from all subjects.

Glucose Tolerance Test

The OGT test was done according to WHO guidelines. All 22 participants followed their normal diet and restricted performance of heavy physical exercise, smoking and caffeine for 3 days before the test. After an overnight fast, each drank a glucose solution (75 g in 200 ml of water) at 09.00 h. Venous blood samples were taken for measurement of plasma glucose (mmol/L), plasma immunoreactive insulin concentration (IRI: pmol/L) and potassium level (mg/dl) during fasting and at 30, 60, 120, and 180 min after the glucose load.³ Plasma samples were stored at -20°C and each sample was assayed for glucose and IRI. Plasma glucose was determined with an autoanalyser using a glucose oxidase method. IRI was assessed by radioimmunoassay using an antihuman insulin antibody.

T Wave Morphology, QT Interval and QT Dispersion on 12-Lead ECG

The QT interval and QRS duration were measured in all leads of a 12-lead ECG recorded at a paper speed of 50 mm/s for 2 consecutive cardiac cycles during fasting and at 30, 60, 120 and 180 min after glucose load.³ The QT (U) interval was defined as the time between the beginning of the QRS complex and the point at which the line of maximal downslope of the T wave [or the late component of the T (U) complex, if present] crossed the baseline before the isoelectric UP interval.¹⁵ None of the 11 healthy volunteers had a U wave superimposed on the terminal portion of T wave. If the T wave could not be reliably determined or if it had a very low amplitude, QT measurements were not obtained, and those leads were excluded from the analysis. The QT interval was measurable in 9–12 leads (mean, 11±1 leads) in each subject. The mean QT interval was calculated as the average of all measurable leads.

QT dispersion, defined as the difference between the maximum and minimum QT intervals, was determined by previously described methods.³ Measurements were obtained during fasting and at 30, 60, 120, and 180 min after the glucose load. Two independent experienced observers who were unaware of the clinical data performed the analysis.

Table 3 T Wave Changes, QT Intervals and QT Dispersion During the Oral Glucose Tolerance Test

	Long QT syndrome (n=11)	Control group (n=11)	p value
Changes in T wave morphology (yes/no)	11/0	0/11	<0.00001
QT maximum (ms)			
Fasting	587±73	422±21	<0.0001
30 min	627±58*	424±25	<0.0000001
60 min	617±76*	423±33	<0.00001
120 min	616±105	420±29	<0.0001
180 min	586±65	420±29	<0.00001
QT minimum (ms)			
Fasting	451±69	389±24	<0.05
30 min	446±63	386±23	<0.05
60 min	445±57	382±25	<0.01
120 min	450±63	383±31	<0.01
180 min	456±59	381±29	<0.01
QT dispersion (ms)			
Fasting	135±65	33±7	<0.001
30 min	179±64**	38±16	<0.0001
60 min	171±53*	40±22	<0.00001
120 min	164±71	37±8	<0.001
180 min	130±63	30±6	<0.001

* $p<0.05$ vs Fasting, ** $p<0.01$ vs Fasting.

Fig 1. Changes in the QT interval and QT dispersion during the oral glucose tolerance test (A) The maximal QT interval in the long QT syndrome and control groups. The maximal QT intervals at 30 and 60 min after glucose load were significantly increased compared with the fasting value in patients with long QT syndrome. * $p<0.05$ vs Fasting. (B) The minimal QT interval in the long QT syndrome and control groups. The minimal QT interval did not change significantly after glucose load in the 2 groups. (C) The QT dispersion in the long QT syndrome and control groups. The QT dispersion at 30 and 60 min after the glucose load was significantly increased and returned to the fasting level in patients with long QT syndrome. * $p<0.05$ vs Fasting, ** $p<0.01$ vs Fasting. Data are mean±SD.

Linear regression analysis yielded minimal intraobserver ($r=0.95$, $p<0.0001$) and interobserver ($r=0.94$, $p<0.0001$) variations. A changes in T wave morphology was defined as a distinctly visible alteration of T wave morphology, such as broad-based, biphasic, bifid or notched T waves and macroscopic T wave alternans.^{12,13,16–19}

Statistical Analysis

Data are expressed as the mean value±SD. The 2-tailed unpaired Student's t test was used for comparison of group mean values expressed as continuous variables. The chi-square test was used to evaluate differences in categorical variables between the 2 groups. Multiple comparisons of continuous variables were performed by ANOVA coupled with Scheffe's test. A p value <0.05 was considered significant.

Results

Responses of Potassium, Glucose and Insulin During the OGT Test (Table 2)

Impaired glucose tolerance was detected in 2 of 11 patients with congenital LQTS and in 2 of 11 control subjects. Diabetes mellitus was not documented in either group. Plasma glucose and IRI after glucose load were significantly higher than during fasting in each group, but there were no significant differences between the 2 groups in potassium level, plasma glucose and IRI during fasting and after glucose load.

Heart Rate, QRS Duration and QT Interval During OGT Test

There was no significant difference between the 2 groups in heart rate (HR) during fasting and after glucose load. In

Fig2. ECG from patient 1 during oral glucose tolerance test before receiving oral β -blocker. (A) T wave morphologies in leads V₁₋₄ changed distinctly after glucose load and ventricular arrhythmias were observed at 30 and 60 min. (B) Enlarged ECGs showed bifid T wave changes in leads V₂ and V₃ at 60 min after glucose load with increased IRI. PG, plasma glucose; IRI, immunoreactive insulin concentration.

Fig3. ECG from patient 5 after oral administration of β -blocker and mexiletine during oral glucose tolerance test. (A) T wave morphologies in leads V₁₋₆ changed distinctly after glucose load and returned to baseline at 180 min. (B) Enlarged ECGs showed biphasic and bifid T wave changes in leads V₂ and V₄ at 60 min after glucose load with remarkable increased IRI.

patients with LQTS, the fasting HR was 60 ± 10 beats/min, and at 30, 60, 120 and 180 min after glucose load, it was 61 ± 8 , 61 ± 8 , 59 ± 10 and 59 ± 10 beats/min, respectively. In control subjects, fasting HR was 61 ± 8 beats/min and at 30, 60, 120 and 180 min after glucose load, it was 61 ± 6 , 62 ± 6 , 62 ± 6 and 60 ± 6 beats/min, respectively.

There was no significant difference in the mean QRS duration during fasting and after glucose load between the LQTS and control groups. In LQTS, the QRS duration during fasting was 80 ± 17 ms and at 30, 60, 120 and 180 min after glucose load, it was 80 ± 18 , 80 ± 17 , 80 ± 19 and 80 ± 17 ms, respectively. In the control group, the QRS duration during fasting was 80 ± 15 ms, and at 30, 60, 120 and 180 min after glucose load, it was 80 ± 17 , 80 ± 16 , 80 ± 16 and 80 ± 15 ms, respectively. The maximal and minimal QT intervals during fasting and after glucose load were significantly higher in the LQTS group. The maximal QT interval

increased significantly after glucose load with recovery to the fasting level after 180 min, but the minimal QT interval was unaffected in the LQTS group (Table 3). Maximal and minimal QT intervals did not change significantly during the OGT test in the control group (Fig 1A,B).

T Wave Change and QT Dispersion During OGT Test

The LQTS group had a higher incidence of changes in T wave morphology after glucose load (11 of 11 patients [100%]) than the control group (0 of 11 [0%]; $p < 0.0001$). Biphasic or bifid (notched) T wave changes became visible after glucose load in all patients with LQTS (Figs 2,3). Both biphasic and bifid T wave changes were observed after glucose load in 4 of the 11 LQTS patients and a broad-based T wave developed after glucose load in 8 patients. The T wave changes returned to the fasting level 180 min after glucose load in 7 of 11 patients (Fig 3). Isolated prema-

Fig 4. ECG from patient 3 during fasting and at 120 min after glucose load during oral glucose tolerance test. T wave alternans (arrows) was observed in leads V3 and V4 at 120 min after glucose load. PG, plasma glucose; IRI, immunoreactive insulin concentration.

ture ventricular contractions and T-wave alternans were observed after glucose load in 3 and 1 patients, respectively (Figs 2, 4). The QT dispersion during fasting and after glucose load was significantly greater in the LQTS group than in the controls. It increased significantly after glucose load and returned to fasting level at 180 min, whereas in the control group there was no significant change in this parameter (Table 3, Fig 1C). In the LQTS group, there was no significant difference between the patients with and without medication in QT dispersion during fasting and after glucose load.

Discussion

We evaluated the relation between plasma insulin level during an OGT test and ventricular repolarization abnormalities in patients with congenital LQTS. T wave morphology changed distinctively with increased IRI after glucose load in all cases in the LQTS group, but not in control group. QT dispersion was also increased after glucose load in patients with LQTS compared with the control group. QT dispersion reflects the regional variation in ventricular repolarization, which provides an electrophysiologic substrate for arrhythmias.^{20–23} These findings suggest that glucose-induced insulin secretion is one of the factors that induces or aggravates abnormalities of repolarization in patients with LQTS, which may increase their susceptibility to ventricular arrhythmias.

Effect of Glucose-Induced Insulin Secretion on Ventricular Repolarization Abnormalities

In our previous study,³ an increased level of IRI correlated with QT dispersion in 20 middle-aged volunteers, but no relation was found between QT dispersion and plasma glucose level. That result suggested that high plasma insulin levels might provoke a widening of regional differences in repolarization of the ventricle. In the present study, we selected age-matched control subjects and the insulin

responses to the OGT test showed similar values in both groups. Only the LQTS group responded with increased QT dispersion during the OGT test, indicating high sensitivity to insulin in ventricular repolarization.

Not only QT dispersion, but also T wave morphologies were affected by glucose-induced insulin secretion in the LQTS group, and the changes returned to the baseline in most cases after 180 min with a concomitant return of the IRI level. A widened or bifurcated T wave, and prolonged QT intervals similar to the present observations have been observed under simulated long QT conditions created by opposing voltage gradients between the epicardium and the M-cell region, and the endocardium and the M-cell region in a canine wedge preparation.^{16,18,19,23} It is not known how insulin affects the different components of the repolarizing currents among the cells in the epi- and endocardium and M-region, where subtle differences in the K^+ and Na^+ currents are present. Recently, Aulbach et al² have shown that insulin stimulates the L-type Ca^{2+} current in isolated rat ventricular myocytes in a dose-dependent manner, although the effects are not so remarkable. If the stimulant action of the L-type Ca^{2+} current by insulin is also observed in human ventricle in the clinical situation, the most pronounced effect would be expected to develop in the M-cell region where opposing outward currents are less than in the other 2 regions. In accordance with this expectation, the maximal QT intervals in the present patients with LQTS were prolonged with increased IRI, but the minimal QT intervals were unchanged. Nevertheless, the maximal QT intervals in the controls did not change significantly. However, the number of control subjects in this study was less than in our previous study in which impaired glucose tolerance was detected in 11 of 20 middle-aged volunteers. The younger aged control group in the present study had low insulin levels within a narrow range compared with the middle-aged volunteers in our previous study,³ so the different responses to insulin between 2 control groups might caused by dose-dependent effects of insulin on the maximal QT interval and QT dispersion. Insulin has been shown to cause hyperpolarization of the membrane potential through activation of the Na^+-K^+ pump,^{24–26} which could also produce a high K^+ gradient across the cell membrane with depletion of K^+ from the narrow extracellular space. Although the serum K^+ concentrations were unchanged after glucose load in both groups in the present study, the possibility that an increased K^+ gradient could affect the repolarization process differently among the 3 regions of the ventricular wall cannot be excluded, and might contribute to the abnormalities observed in LQTS. The cellular basis for these abnormalities produced by insulin needs to be further explored.

Clinical Implications

Molecular identification of the gene responsible for QT prolongation has disclosed a wide spectrum of clinical manifestations.^{8–12} Some sporadic cases of nonfamilial LQTS have exhibited a distinct gene defect²⁷ and some cases of drug-induced LQTS, which is believed to be an acquired form, have a subtle genetic abnormality that only manifests as QT prolongation with the taking of drugs.²⁸ Therefore, the importance of genetic screening for patients with concealed QT prolongation is now widely recognized, although it is still a research-oriented examination and not available to every patient on a clinical basis.

On the other hand, the OGT test is an easy and widely

used method, with which a high incidence of repolarization abnormalities can easily be detected and thus provide a good provocation test for selecting those patients requiring genetic screening.

The QT prolongation and ST-T changes in patients with LQTS may fluctuate from time to time and can not be predicted because of the multiple factors influencing ventricular repolarization and the different gene defects with their variable phenotypic expressions. High plasma insulin levels are another factor that aggravate ST-T changes and QT dispersion, but there have not been any reports of increased incidence and development of torsades de pointes after food intake. Further careful follow-up in a large-scale study is necessary to clarify the clinical significance of the insulin effects observed in the present study.

Study Limitations

The genetic defects in LQTS involved in 2 different K⁺ and Na⁺ channels,⁴⁻⁷ creating different ionic bases of the QT prolongation. The genetic basis of the present patients was not known except for 2 cases that had a mutation in HERG (LQT2: patients 5 and 8). Although none of other 9 cases showed the T-wave morphology typical of LQT3 according to Moss et al;²⁹ it was not known whether they presented abnormalities in the rapid (I_{Kr}) or slow (I_{Ks}) components of the delayed rectifier K⁺ or Na⁺ channels, and whether the changes observed were specific gene-related phenomena or not. Therefore, the relationship between repolarization abnormalities occurring during the OGT test and the genotype of patients with LQTS remains to be evaluated.

Conclusions

A high insulin level after glucose load in patients with LQTS was associated with further QT prolongation, increased QT dispersion and changes in T wave morphology. Glucose-induced insulin secretion may play a role in the abnormalities and inhomogeneity of repolarization, provoking increased susceptibility to ventricular arrhythmias. Further study is required to clarify its clinical significance and the ionic mechanisms.

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