The relationship between blood glucose level and QTc duration in the critically ill

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ABSTRACT

Objective: To determine whether hyperglycaemia is associated with prolongation of the corrected QT (QTc) interval on the electrocardiogram (ECG) in critically ill patients.

Design: Single-centre, prospective observational study.

Participants and setting: 197 consecutive patients admitted to the adult intensive care unit of a 570-bed teaching hospital over 10 weeks from November 2004.

Main outcome measures: Correlation between QT interval (on standard 12-lead ECG taken on ICU admission, corrected with Bazett's formula) and serum glucose level (BGL) in blood collected at time of ECG; comparison of variables, including BGL, by QTc category (≤ 0.44 s or > 0.44 s); explained variance (R^2) of QTc, determined by multivariate regression analysis.

Results: Mean patient age was 53.4 years. A moderate, positive correlation was found between QTc and BGL (Pearson's correlation coefficient, $r = 0.277$, $P < 0.001$). A standard multivariate regression model explained 32.9% (R^2) of QTc variance, and revealed four significant, independent predictors of QTc duration: heart rate (explaining 11.4% of QTc variance), use of inotropes (10.1%), BGL (7.3%) and serum magnesium level (4.6%). In the cohort with QTc > 0.44 s, BGL was significantly higher, as were the need for inotropes, APACHE II scores and mortality. QTc was significantly longer in patients with BGL > 8 mmol/L than in those with lower BGL (0.471 v 0.442 s, $P < 0.001$). The only independent predictors of mortality were APACHE II score and mean arterial pressure.

Conclusions: There was a moderate, significant correlation between QTc and BGL. Patients with a QTc > 0.44 s had higher BGL, APACHE II score and mortality. BGL was an independent predictor of QTc duration, but neither BGL nor QTc were independent predictors of mortality in this study.

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The QT interval on the electrocardiogram (ECG) represents the time during which there is depolarisation and subsequent repolarisation of the ventricle. It is an index of the myocardial refractory period and of arrhythmogenic potential.[1] Increased risk of arrhythmias starts to be a concern at a corrected QT (QTc) interval over 0.440 seconds.[2] QTc has been shown to be prolonged in healthy people with acute hyperglycaemia[3] or with high fasting blood glucose levels.[4,5] The prolongation of QTc interval is associated with an increased incidence of sudden death in patients with long QT syndrome,[6] myocardial infarction,[7] left ventricular systolic dysfunction[8,9] and diabetes,[10] and in apparently healthy people.[11,12]

Hyperglycaemia is common in critically ill patients, even in the absence of diabetes mellitus.[13] Poor glycaemic control is associated with a higher incidence of morbidity and mortality in the critically ill.[14,15] It has been suggested that a blood glucose level (BGL) of < 8 mmol/L should be targeted in management of the critically ill.[15]

The objective of this study was to determine whether an elevated BGL was independently associated with prolongation of the QTc interval in critically ill patients.

Methods

Study population

We undertook a prospective study of all patients admitted to the intensive care unit of the Gold Coast Hospital, a 570-bed tertiary teaching hospital in Queensland, during a 10-week period from 2 November 2004. The study was approved by the Research Ethics Committee of the hospital.

All patients aged over 15 years who were admitted to the ICU during the trial period were considered eligible for the study. Exclusion criteria included a previously documented history of prolonged QTc interval.

During the 10-week study period, 200 patients were admitted to the ICU. Of these, three were excluded from the trial: one was younger than 15 years, and the families of the other two refused consent.

Power analysis

The number of participants required for the study was determined using a power of 0.80, an α value of 0.05, and an effect size (r) of 0.20. As no previous studies have quantified the extent of correlation between hyperglycaemia and QTc duration, the effect size was determined using the convention suggested by Cohen,[16] with an r value of 0.20 representing a small to moderate correlation. Using the above parameters, the number of patients required in the study to detect an effect size of 0.20 was 200.

Table 1. Relationship between patient variables and QTc interval

Variables entered in analysis*	*n*	Correlation with QTc†	*P*‡
Continuous variables			
Age	188	0.19	< 0.01
Pulse rate	188	0.34	< 0.001
Mean arterial pressure	186	0.02	ns
Temperature	186	–0.08	ns
Serum concentration of			
Glucose	179	0.27	< 0.001
Sodium	187	–0.05	ns
Potassium	187	0.15	0.05
Troponin I	173	0.05	ns
Magnesium	163	0.21	< 0.01
Calcium	168	–0.04	ns
APACHE II score	188	0.31	< 0.001
Categorical variables		**QTc (s)**	
Total group	188	0.45	
Sex			
Male	115	0.45	ns
Female	73	0.451	
Arrhythmias			
No	184	0.45	ns
Yes	2	0.447	
Insulin infusion			
No	180	0.449	ns
Yes	6	0.486	
Inotrope infusion			
No	169	0.446	< 0.001
Yes	17	0.498	
History of IHD			
No	152	0.447	ns
Yes	35	0.46	
History of diabetes mellitus			
No	167	0.447	0.01
Yes	20	0.475	
Type of admission			
Surgical	60	0.439	ns
Neurosurgical	60	0.446	
Medical	68	0.525	

QTc = corrected QT interval. ns = not significant.
APACHE = Acute Physiology and Chronic Health Evaluation.
IHD = ischaemic heart disease.
* Multivariate regression analysis; history of diabetes was not included in the multivariate analysis as it was closely associated with presence of an insulin infusion.
† Pearson correlation coefficient.
‡ *P* based on Pearson's correlation coefficient for continuous variables, independent *t* test for comparisons with two categories, and ANOVA for three categories.

Data collection

A standard 12-lead ECG was recorded for each patient on the day of ICU admission. ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV. QT intervals were manually measured on the lead II trace using magnification, as U waves are least prominent on the trace from this lead.[17] However, when the T wave was poorly defined in lead II, lead V_2 was used.[18] The QT interval was measured from the beginning of the QRS complex to the end of the T wave, based on previous findings that measurement from the Q wave to the apex of the T wave, although methodologically simple, fails to include any disease-induced variability in the interval T_{apex} to T_{end}.[19] In the presence of U waves, the QT interval was measured from the beginning of the QRS complex to the nadir of the curve between the T and U waves. To maximise consistency in QT measurements, they were performed by a single reader (E B),[1] who was blinded to all other results at the time of measurement. The QT interval was corrected for rate using Bazett's formula ($QTc = QT/\sqrt{R–R}$), where R–R is the interval (in seconds) measured from the onset of the QRS complex from which the QT interval was measured until the onset of the following QRS.[20]

At the time the ECG was taken on admission, blood samples were collected for measurement of blood glucose, sodium, potassium, magnesium, calcium and troponin I levels. Pulse rate, mean arterial blood pressure (MAP) and temperature were also documented at that time, and it was noted whether the patient was receiving infusions of insulin, inotropes or drugs known to affect QTc duration. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system.

Data analysis

The strength of the linear relationships between QTc and all continuous variables, including BGL, was tested using the Pearson correlation coefficient (assumptions of normality were not violated).

Multiple regression analysis was performed to create a predictive model in which QTc was the dependent variable. Standard conditions for multiple regression analysis were met, with an acceptable sample size, minimal outliers and no violations in the assumptions of normality. The regression included 17 clinical variables measured on admission to the ICU (see Table 1) as independent variables. A history of diabetes was not included in the multivariate analysis model as it was highly associated with the presence of an insulin infusion. Results of the multiple regression analysis are given as percentage of unique variance (R^2) in QTc that is explained by the model, and by any of the independent variables. Student's *t* test and ANOVA were performed to compare means for continuous variables between groups.

Table 2. Characteristics of total study population and by duration of QTc

	All participants ($n = 197$)		QTc ⩽ 0.44 s ($n = 81$)		QTc > 0.44 s ($n = 116$)	
	n	% or mean (95% CI)	*n*	% or mean	*n*	% or mean
Sex	197		81		116	
Male		61.4%		59.3%		62.9%
Female		38.6%		40.7%		37.1%
Age, years	197	53.4 (50.8–56.0)	81	51.6	116	54.6
APACHE II	197	13.5 (12.4–14.6)	81	11.6	116	14.8*
Vital signs					108	
MAP (mmHg)	188	91.5 (89.4–93.6)	80	90.7		92.1
Heart rate (beats/min)	189	83.2 (79.7–86.6)	81	75.8		88.6†
Temperature (° C)	188	36.6 (36.5–36.7)	80	36.7		36.5
Serum levels						
Glucose (mmol/L)	185	7.8 (7.3–8.3)	76	6.8	109	8.5†
Sodium (mmol/L)	194	142.5 (142–143)	81	142.6	113	142.2
Potassium (mmol/L)	194	4.2 (4.1–4.3)	81	4.1	113	4.2
Magnesium (mmol/L)	169	0.80 (0.78–0.83)	70	0.78	99	0.82
Calcium (mmol/L)	174	2.28 (2.26–2.30)	71	2.29	103	2.27
Troponin I (μg/L)	180	3.26 (–1.8–8.3)	73	0.01	107	5.49
History of	189		81		108	
Ischaemic heart disease		17.8%		16.0%		20.4%
Diabetes mellitus		10.2%		4.9%		14.8%*
Admission type	197		81		116	
Surgical		32.5%		33.3%		31.9%
Neurosurgical		31.5%		37.0%		27.6%
Medical		36.0%		29.6%		40.5%
Presence of	188		80		108	
Insulin infusion		3.0%		1.3%		4.6%
Inotrope infusion		8.6%		3.8%		13.0%‡
Arrhythmias		1.0%		1.3%		0.9%
Length of stay (days)						
ICU stay	197	3.4 (2.7–4.0)	81	3.1	116	3.5
Hospital stay	193	18.2 (13.2–23.1)	80	16.3	113	19.5
Mortality						
In ICU	197	8.1%	81	2.5%	116	12.1%‡
In hospital	193	12.2%	80	6.3%	113	16.8%‡

QTc = corrected QT interval. 95% CI = 95% confidence interval of the mean.
APACHE = Acute Physiology and Chronic Health Evaluation. MAP = mean arterial blood pressure.
* $P < 0.01$, † $P < 0.001$, ‡ $P < 0.05$, independent *t* test for continuous variables and Pearson χ^2 for categorical variables.

Multivariate odds ratios (ORs) for mortality were determined by logistic regression, with inclusion of all predictive variables for both ICU and hospital mortality.

Subgroup analyses were performed with both the inclusion and exclusion of patients taking drugs known to prolong QTc, with no significant difference in results found between the two groups. An α value less than 0.05 was deemed statistically significant. All analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Ill, USA).

Results

A total of 197 patients were enrolled in the study. Their descriptive characteristics are summarised in Table 2. Just over 60% were men, and the average age was 53.4 years. The mean APACHE II score was 13.5 (range, 1–44).

Few data were missing, with less than 5% of values missing for most variables; serum troponin I (8.6%), serum calcium (11.7%) and serum magnesium (14.2%) levels had the highest rates of missing data.

Just over a third of ICU admissions had a primarily medical diagnosis; the other two-thirds were equally divided between neurosurgical diagnoses and other surgical diagnoses. Eighteen patients died in the ICU, with six further deaths subsequent to discharge from the ICU to a ward.

QTc interval and blood glucose level

There was a moderate, positive relationship between QTc and BGL (Pearson's correlation, $r = 0.277$, $P < 0.001$). Table 1 shows the correlation of QTc with all other variables. Independent variables significantly correlated with QTc included age, heart rate, BGL, serum magnesium level, serum potassium level and APACHE II score. The QTc interval was significantly longer in patients receiving an inotrope infusion than in those not receiving inotropes.

Table 2 summarises the demographic variables for the study population, and compares the patients with a QTc ⩽ 0.44 s with those with a longer QTc. On admission to the ICU, the QTc was prolonged (> 0.44 s) in 107 patients (54%). In this group, APACHE II scores, heart rate and BGL were significantly higher than in patients with a QTc ⩽ 0.44 s. ICU and hospital mortality were also significantly higher, as was the proportion with diabetes mellitus and the proportion receiving inotrope infusions.

In patients with BGL > 8 mmol/L, QTc was significantly longer than in those with BGL ⩽ 8 mmol/L (0.471 s [95% CI, 0.459–0.483] v 0.442 s [95% CI, 0.434–0.450]; $P < 0.001$). Similarly, patients with BGL > 8 mmol/L had a higher APACHE II score than patients with a BGL ⩽ 8 mmol/L (15.9 [95% CI, 13.9–17.9] v 12.1 [95% CI, 10.9–13.3]; $P = 0.001$).

Predictors of QTc duration

In standard multiple regression analysis, the Omnibus tests of model coefficients demonstrated a good model fit ($P < 0.005$). The model explained 32.9% of variance (R^2) in QTc. Four of the 17 independent variables were found to contribute uniquely and significantly to the prediction of QTc duration. Heart rate was the strongest independent contributor to the model, followed by use of inotropes, BGL and serum magnesium level (Table 3).

Predictors of survival

The QTc was found to be significantly longer in patients who died in hospital compared with those who survived to hospital discharge (0.487 s [95% CI, 0.464–0.510 s] v 0.445 s [95% CI, 0.438–0.452 s]; $P < 0.001$) (Table 4). Those who died in hospital also had a higher BGL on admission (9.1 mmol/L; 95% CI, 7.7–10.4) than those who survived (7.6 mmol/L; 95% CI, 7.1–8.2), although this difference was not statistically significant ($P = 0.07$). Not surprisingly, Table 4 shows that patients who survived their hospital stay were significantly younger, had significantly higher MAP

Table 3. Independent predictors of QTc duration*

	% of QTc variance explained	*P*
Heart rate	11.4%	< 0.001
Presence of inotrope infusion	10.1%	< 0.01
Serum glucose	7.3%	0.05
Serum magnesium	4.6%	0.03

QTc = corrected QT interval.
* Based on standard multivariate regression using 17 variables.

Table 4. Characteristics of study population by mortality

	Died in hospital (*n* = 24)		Survived to discharge (*n* = 169)	
	n	% or mean	*n*	% or mean
Sex	24		169	
Male		50%		62%
Female		50%		38%
Age (years)	24	61.7	169	52.1*
APACHE II score	24	23.6	169	12.0†
Vital signs	23			
MAP (mmHg)		84.9	163	92.4*
Heart rate (beats/min)		95.4	164	81.6*
Temperature, (°C)		36.2	163	36.6*
QTc (s)	23	0.487	163	0.445†
Serum levels				
Glucose (mmol/L)	22	9.1	159	7.6
Sodium (mmol/L)	23	142.1	167	142.6
Potassium (mmol/L)	19	4.2	167	4.2
Magnesium (mmol/L)	19	0.84	146	0.8
Calcium (mmol/L)	20	2.28	150	2.28
Troponin I (μg/L)	22	21.7	154	0.71
History of	23		164	
IHD		30%		17%
Diabetes mellitus		13%		10%
Admission type	24		181	
Surgical		8%		36%
Neurosurgical		54%		29%‡
Medical		38%		35%
Presence of	23		163	
Insulin infusion		9%		3%
Inotrope infusion		30%		6%†
Arrhythmias		4%		0.6%
Length of stay (days)	24		169	
ICU stay		4		3.1
Hospital stay		10.2		19.3

APACHE = Acute Physiology and Chronic Health Evaluation.
MAP = mean arterial blood pressure.
QTc = corrected QT interval.
IHD = ischaemic heart disease.
* $P < 0.05$, † $P < 0.001$, ‡ $P < 0.01$, independent *t* test for continuous variables and Pearson χ^2 for categorical variables.

Table 5. Factors associated with survival

Significant predictor*	Odds ratio for hospital survival (95% CI)†
APACHE II (per 1 point increase)	0.76 (0.66–0.88)‡
MAP (per 1 mmHg decrease)	0.93 (0.87–0.99)§

APACHE = Acute Physiology and Chronic Health Evaluation.
MAP = mean arterial blood pressure.
* Significant factor as predicted by forward logistic regression analysis.
† Odds ratio (OR) > 1 represents higher likelihood of survival.
OR < 1 represents lower likelihood of survival (increased mortality).
‡ $P < 0.001$. § $P < 0.05$.

and temperature, as well as a significantly lower heart rate and APACHE II score. Among the survivors, there was a significantly lower proportion of neurosurgical admissions and of patients receiving inotrope infusions.

The logistic regression model for hospital survival indicated that APACHE II and MAP were significant predictors of survival. On the basis of the Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 5.9$, df = 8, $P = 0.66$ for hospital survival), both models fit the data well. Table 5 reports the multivariate odds ratios.

Discussion

This study identified that, in critically ill patients, BGL is an independent predictor of the QTc interval, together with heart rate, use of inotrope infusion and serum magnesium level. A small to moderate, but significant, correlation between BGL and QTc was found, and patients with a QTc interval > 0.44 s had a significantly higher BGL than patients with QTc ⩽ 0.44 s. Heart rate, APACHE II score and mortality were also significantly higher in patients with a prolonged QTc. Furthermore, APACHE II scores and MAP were independent predictors of mortality.

Our study explored the relationship between QTc and hyperglycaemia in the critically ill. In critical care patients, hyperglycaemia is already known to be associated with increased mortality.[14] This was supported by our data, as there was a trend that patients who died during their hospital stay had a higher BGL on ICU admission than patients who survived to hospital discharge. The study confirmed established risk factors of mortality, such as older age, higher APACHE II score, low MAP, rapid heart rate and requirement for inotropes.

In patients who died, QTc was prolonged, and APACHE II scores were significantly higher. In addition, there was a significant, positive correlation between QTc duration and APACHE II score, with significantly higher APACHE II scores in those with a QTc > 0.44 s. Similarly, those with a BGL > 8.0 mmol/L also had significantly higher APACHE II scores. This may reflect the relation between QTc and hyperglycaemia. Alternatively, it may be that both hyperglycaemia and prolonged QTc are surrogate markers of illness severity.

Thus, it is important to emphasise that these results do not show a causative link between hyperglycaemia and prolonged QTc. However, potential mechanisms by which glucose may affect QTc have been suggested. Zhang et al[21] found that hyperglycaemia results in overproduction of reactive oxygen species, and that these in turn reduce function of the human ether-à-go-go-related gene (HERG) potassium channel, the major molecular contributor to the delayed rectifier potassium current that is responsible for cardiac repolarisation. HERG channel dysfunction is known to contribute more than 40% of mutation-based long QT syndrome.[22] Glucose has been found to modulate HERG current amplitude and activation voltage, with hyperglycaemia resulting in depressed HERG function — this in turn results in prolongation of the QT interval.[21] Alternatively, Marfella et al[23] suggested that the increase in cytosolic calcium content purported to occur in healthy people during oral glucose testing may be responsible for the QTc prolongation seen with hyperglycaemia.

Our study had a number of limitations. Any study involving measurement of QTc has the potential for measurement error. There is dispute in the literature as to whether manual[24] or automated[25] measurements of QT interval are more accurate. However, with either approach (and in our study), reproducibility is optimised by using one ECG reader, allowing uniform application of procedures.[1]

Bazett's formula was used to correct QT interval for heart rate, as it has been validated previously as a correction measure in diagnosis of long QT syndrome,[26] and is the most widely used formula for correcting QT interval in population-based studies of QTc as a predictor of outcome.[11] However, others have argued[27] that subject-specific heart rate correction methods are superior to the standardised methods of Bazett and Fridericia.

Different cut-off values for QTc have been proposed, including 0.44 s and 0.46 s.[28] Both values pose challenges, either under- or overdiagnosing prolonged QTc. In this study, the most conservative cut-off was chosen, so as not to miss any mortality where QTc might have played a role. Furthermore, missing values lessen the reliability of multiple regression. However, our study had between 1.5% and 14% of data missing, depending on the variable, which we considered acceptable.

A multitude of factors may influence QTc, not all of which were adjusted for in our analysis. Factors known to influence QTc that were not accounted for include:

- Congenital factors.[29] Most patients did not have a previous ECG available, but none were documented to have a previous diagnosis of long QT syndrome.

- Diurnal variability in QTc.[30] Timing of the ECG was dictated by time of ICU admission and hence was not uniform.
- Central nervous system abnormalities.[31,32] Due to the heterogeneity of the diagnoses, subgroup analyses of patients with central nervous system abnormalities were limited to the type of admission (surgical, neurosurgical or medical) in multivariate and logistic regression analyses.

Conclusions

BGL is an independent predictor of QTc interval in critically ill patients. The relationship between glucose and QTc interval requires further exploration to determine whether glucose is causally linked to QTc prolongation and, if so, whether this contributes to the observed higher mortality of critically ill patients with hyperglycaemia.

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References

1 Bednar M, Harrigan E, Anziano R, et al. The QT interval. *Prog Cardiovasc Dis* 2001; 43 Suppl: 1-45.
2 Morganroth J, Brozovich FV, McDonald JT, Jacobs RA. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. *Am J Cardiol* 1991; 67: 774-6.
3 Marfella R, Nappo F, De Angelis L, et al. The effect of acute hyperglycaemia on QTc duration in healthy men. *Diabetologia* 2000; 43: 571-5.
4 Lefrandt J, Diercks G, Van Boven A, et al. High fasting glucose and QTc duration in a large healthy cohort (comment). *Diabetologia* 2000; 43: 1332-3.
5 Leotta G, Maule S, Rabbia F, et al. Relationship between QT interval and cardiovascular risk factors in healthy young subjects. *J Hum Hypertens* 2005; 19: 623-7.
6 Jervell A, Lange-Nielsen F. Congenital deaf mutism: functional heart disease with prolongation of QT interval and sudden death. *Am Heart J* 1957; 54: 59-68.
7 Peters RW, Byington RP, Barker A, Yusuf S. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. J *Clin Epidemiol* 1990; 43: 167-72.
8 Padmanabhan S, Silvet H, Amin J, Pai R. Prognostic value of QT interval and QT dispersion in patients with ventricular systolic dysfunction: results from a cohort of 2265 patients with an ejection fraction of ⩽ 40%. *Am Heart J* 2003; 145: 132-8.
9 Vrtovec B, Delgado R, Zewail A, et al. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Circulation* 2003; 107: 1764-9.
10 Naas A, Davidson N, Thompson C, et al. QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study. *BMJ* 1998; 316: 745-6.
11 Schouten EG, Dekker JM, Mepplink P, et al. QT-interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* 1991; 84: 1516-23.
12 Robbins J, Nelson J, Rautaharju P, Gottdiener J. The association between the length of the QT interval and mortality in the cardiovascular health study. *Am J Med* 2003; 115: 689-94.
13 Montori VM, Bistrain BR, McMahon MM. Hyperglycaemia in acutely ill patients. *JAMA* 2002; 288: 2167-9.
14 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-67.
15 Finney S, Zekveld C, Elia A, Evans T. Glucose control and mortality in critically ill patients. *JAMA* 2003; 290: 2041-7.
16 Cohen J. Statistical power analysis for the behavioural sciences. Hillsdale, NJ: Erlbaum, 1988.
17 Garson A. How to measure the QT interval — what is normal? *Am J Cardiol* 1993; 72: 14B-6B.
18 Elming H, Sonne J, Lublin H. The importance of the QT interval: a review of the literature. *Acta Psychiatr Scand* 2003; 107: 96-101.
19 Davey P. QT interval measurement: Q to T_{apex} or Q to T_{end}? J *Intern Med* 1999; 246: 145-9.
20 Bazett HC. An analysis of time-relations of electrocardiograms. *Heart* 1920; 7: 353-67.
21 Zhang Y, Han H, Wang J, et al. Impairment of human ether-a-go-go-related gene (HERG) K+ channel function by hypoglycemia and hyperglycemia. Similar phenotypes but different mechanisms. *J Biol Chem* 2003; 278: 10417-26.
22 Modell S, Lehmann M. The long QT syndrome family of cardiac ion channelopathies — a HuGE review. *Genet Med* 2006; 8: 143-55.
23 Marfella R, Quagliaro L, Nappo F, et al. Acute hyperglycemia induces an oxidative stress in healthy subjects. *J Clin Invest* 2001; 108: 635.
24 Woosley R, Sale M. QT interval: a measure of drug action. *Am J Cardiol* 1993; 72: 36B-43B.
25 Willems J, Abreu-Lima C, Arnaud P, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991; 325: 1767-73.
26 Brouwer J, Van Den Berg M, Grobbee D, et al. Diagnostic performance of various QTc interval formulas in a large family with long QT syndrome type 3: Bazett's formula not so bad after all. *Ann Noninvasive Electrocardiol* 2003; 8: 269-74.
27 Desai M, Li L, Desta Z, et al. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2003; 55: 511-7.
28 Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. *Circulation* 1993; 88: 782-4.
29 Wang Q, Chen Q, Towbin JA. Genetics, molecular mechanisms and management of long QT syndrome. *Ann Med* 1998; 30: 58-65.
30 Bonnemeier H, Wiegand U, Braasch W, et al. Circadian profile of QT interval and QT interval variability in 172 healthy volunteers. *PACE* 2003; 26 Pt II: 377-82.
31 Fukui S, Katoh H, Tsuzuki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. *Crit Care* 2003; 7: R7-11.
32 Van den Bergh W, Algra A, Rinkel G. Electrocardiographic abnormalities and serum magnesium in patients with subarachnoid hemorrhage. *Stroke* 2004; 35: 644-8. ❑