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. Increased risk of arrhythmias starts to be a concern at a corrected QT (QTc) interval over 0.440 seconds. QTc has been shown to be prolonged in healthy people with acute hyperglycaemia or with high fasting blood glucose levels. The prolongation of QTc interval is associated with an increased incidence of sudden death in patients with long QT syndrome, myocardial infarction, left ventricular systolic dysfunction and diabetes, and in apparently healthy people.

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

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, 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.

ABSTRACT

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


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 (R²) 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% (R²) 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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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. However, when the T wave was poorly defined in lead II, lead V2 was used. 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_{\text{apex}} to T_{\text{end}}. 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), 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/R–R), where R–R is the interval (in seconds) measured from the onset of the QRS complex 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.

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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.

Table 1. Relationship between patient variables and QTc interval
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 inotropic 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 those 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...
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 between BGL and QTc was found, and patients with a QTc level. A small to moderate, but significant, correlation between QTc duration and heart rate, APACHE II score and mortality. Furthermore, APACHE II scores and MAP were independent predictors of QTc prolongation seen with hyperglycaemia. 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 found that hyperglycaemia results in overproduction of reactive oxygen species, and that these in turn reduce function of the human ether-a-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. 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. Alternatively, Marfella et al 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 or automated 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.

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, and is the most widely used formula for correcting QT interval in population-based studies of QTc as a predictor of outcome. However, others have argued 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. 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. 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