Glycemia and Corrected QT Interval Prolongation in Young Type 1 Diabetic Patients

What is the relation?

BERT SUYS, MD[1,2]
SARA HEUTEN, MD[1]
DANIEL DE WOLF, MD, PHD[1,2]
MARC VERHERSTRAETEN, ENG[3]
LIEVE OP DE BEECK, ENG[4]
DIRK MATTHYS, MD, PHD[2]
CHRISTIAAN VRINTS, MD, PHD[3]
RAOUL ROOMAN, MD, PHD[4]

The relationship between a prolonged QT interval and an increased risk of sudden death has been extensively explored in familial long QT syndrome, sudden infant death, and ischemic heart disease (1–3). Several recent studies also describe the relation between corrected QT interval (QTc) prolongation, diabetes complications, and an increased mortality in adults (4,5). We recently described QTc prolongation and a larger QT dispersion in a cohort of children and adolescents with type 1 diabetes (6). The influence of changes in glycemia on the length of the QT or QTc remains a controversial issue. Experimental hypoglycemia and, just recently, spontaneous clinical episodes of hypoglycemia proved to lead to QTc lengthening (7–9). There is some evidence that prolonged cardiac repolarization contributes to sudden death associated with nocturnal hypoglycemia in young people with diabetes (10–13). On the other hand, a relation between hyperglycemia and abnormal cardiac repolarization has also been described (14). We therefore simultaneously recorded QT and QTc values using 24-h Holter registration and glucose levels with a continuous glucose monitoring system in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Nine children and adolescents with stable type 1 diabetes (five males and four females aged 9–19 years) were prospectively recruited from the patient population that regularly attends the Diabetes Clinic for Children and Adolescents of the Antwerp University Hospital. Diabetes duration varied between 1 and 9 years with a median of 6 years. All of the patients were treated with a basal-bolus insulin regimen with at least four subcutaneous injections daily. Exclusion criteria were the presence of other disorders, medication known to modify QT, obvious clinical complications or signs of persistent microalbuminuria (albumine excretion >15 μg/min in an overnight timed urine collection), and neuropathy or proliferative retinopathy.

A 24-h electrocardiogram (Dynacord 423; Delmar-Reynolds, Hertford, U.K.) was recorded in each patient, with automatic QT, RR interval, and QTc measurements ($QTc = QT/\sqrt{RR}$). The automatic electrocardiogram analysis provided hourly mean values for heart rate, QT, and QTc together with minimum and maximum values. Simultaneously, interstitial glucose concentrations (IGC) were measured via a subcutaneous abdominal catheter using a continuous glucose monitoring system (CGMS) (Minimed; Medtronic, Minneapolis). This technique provides 12 glucose measurements hourly. The system was calibrated first against standard glucometer values.

Statistical analysis

Calculations were performed using SPSS v.11 statistical software. The Holter datasets are presented as means with minimum and maximum values. Spearman's correlation analysis was used to evaluate the relation between QTc values and glucose concentrations for the patients individually. $P \leq 0.05$ was considered statistically significant.

RESULTS — Holter data were available in all nine patients. CGMS data were lost in one patient due to a technical problem. High values for QT and QTc were found in these patients, with a percent QTc >440 ms up to 56% per hour in one patient and a percent QTc >460 ms up to 31% per hour in another patient. QTc values >550 ms were measured in four of nine patients. The lowest IGC values were found during the night and early morning and the highest concentrations at daytime. The opposite curve was observed for the QTc pattern over 24 h, with the higher QTc values at night and in the early morning (e.g., patient 3 in Fig. 1*A*).

When the correlations were calculated for the patients individually, a strongly significant correlation between QT and glycemia was found in five of eight patients and between QTc and QTc_{max} and glycemia in three of eight patients (Fig. 1*B*).

CONCLUSIONS — In this study, we confirmed that young type 1 diabetic patients have important QTc prolongation, with QTc values up to 578 ms. QTc values above the normal limit of 440 ms were frequent (up to 56% per hour in one patient and >460 ms up to 31% per hour in another patient). The critical QTc value that confers particular vulnerability to ventricular arrhythmias probably varies

From the [1]Department of Congenital and Pediatric Cardiology, University Hospital Antwerp, Antwerp, Belgium; the [2]Department of Congenital and Pediatric Cardiology, University of Ghent, Ghent, Belgium; the [3]Department of Cardiology, University Hospital Antwerp, Antwerp, Belgium; and the [4]Department of Pediatric Endocrinology, University Hospital Antwerp, Antwerp, Belgium.

Address correspondence and reprint requests to Dr. B. Suys, Congenital and Pediatric Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. E-mail: bert.suys@uza.be.

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Abbreviations: CGMS, continuous glucose monitoring system; IGC, interstitial glucose concentration; QTc, corrected QT interval.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

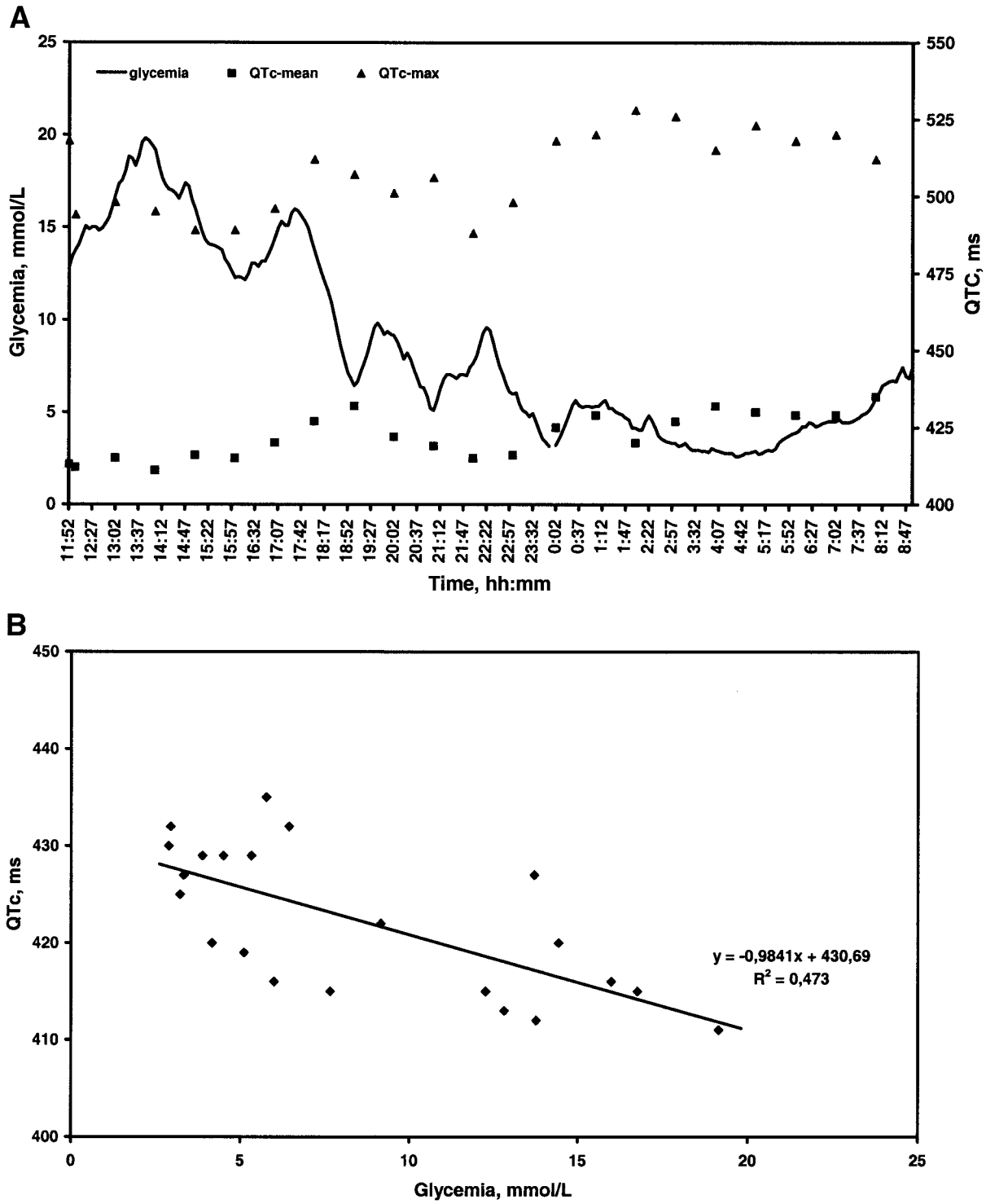

Figure 1— A*: Simultaneous tracings of QTc mean per hour, QTc_{max}, and IGC values.* B*: Individual correlation mean QTc per hour versus glycemia in patient 3* (r = *0.672;* P = *0.003).*

individually but is considered to be ~550 ms (15). Four of nine patients in this study exceeded this threshold.

We also evaluated the relation between IGC and QT or QTc combining Holter recordings and continuous glucose monitoring with an abdominal subcutaneous catheter. A significant correlation was found between QT, QTc, and QTc_{max} and IGC in some patients, with the higher QT and QTc values coinciding with lower glucose readings.

Although CGMS readings are imperfect reflections of glycemia (due to time lag, intersensor variability, and reliability in identifying true hypoglycemia), they make it possible to measure the relationship of glucose to QT over longer periods without disturbing the sleep pattern (16). Our results are in agreement with other reports that describe an abnormal repo-

larization during both experimental and spontaneous clinical nocturnal hypoglycemia (7–9,17). Those data indicated that hypoglycemia can cause an acquired long QT syndrome. Some studies associated unexpected sudden deaths in young diabetic patients (the "dead in bed" syndrome) with cardiac dysrhythmias following abnormal cardiac repolarization during hypoglycemia (10–13). It is not clear whether hypoglycemia and the concomitant reactive adrenergic stimulation per se or rather insulin itself creates this prolonged repolarization. Recently, Robinson et al. (8) induced an acquired long QT syndrome during experimental hypoglycemia in normal men that could be prevented by β-blockade rather independently of extracellular potassium. Murphy et al. (9) showed in a young type 1 diabetic population that a prolonged QTc occurred more frequently during spontaneous overnight hypoglycemia, possibly related to insulin-induced hypokalemia. In our study with simultaneous IGC and QTc measurements, we confirm that the highest QTc values are seen at night and in the early morning, when glucose values are low, due to the treatment scheme. The "dead in bed" syndrome could be explained by a physiologically longer cardiac repolarization at night and thus an electrically instable myocardium, worsened by the hypoglycemia-induced adrenergic stimulation (18), maybe in combination with insulin-induced hypokalemia. When extra medication that prolongs the QT interval or alcohol is taken, the risk for a potentially lethal degree of QT prolongation and fatal arrhythmias will increase. Further work in a larger population is absolutely necessary to explain a mechanism that possibly causes sudden death in young people.

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References

1. Schwartz PJ: Idiopathic long QT syndrome: progress and questions. *Am Heart J* 19: 399–411, 1982
2. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticoni F, Rosti D, Salice P: Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med* 338:1709–1714, 1998
3. Schwartz PJ, Wolf S: QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 57:1074–1077, 1978
4. Veglio M, Sivieri R, Chinaglia A, Scaglioni L, Cavallo-Perin P: QT interval prolongation and mortality in type 1 diabetic patients. *Diabetes Care* 23:1381–1383, 2000
5. Rossing P, Breum L, Major-Pedersen A, Sato A, Winding H, Pietersen A, Kastrup J, Parving HH: Prolonged QTc interval predicts mortality in patients with type 1 diabetes mellitus. *Diabet Med* 18:199–205, 2001
6. Suys BE, Huybrechts SJ, De Wolf D, Op De Beeck L, Matthys D, Van Overmeire B, Du Caju MV, Rooman RP: QTc interval prolongation and QTc dispersion in children and adolescents with type 1 diabetes. *J Pediatr* 141:59–63, 2002
7. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR: Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. *Diabetes* 52:1469–1474, 2003
8. Robinson RT, Harris ND, Ireland RH, Macdonald IA, Heller SR: Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with type 1 diabetes. *Diabetologia* 47:312–315, 2004
9. Murphy NP, Ford-Adams ME, Ong KK, Harris ND, Keane SM, Davies C, Ireland RH, MacDonald IA, Knight EJ, Edge JA, Heller SR, Dunger DB: Prolonged cardiac repolarisation during spontaneous nocturnal hypoglycaemia in children and adolescents with type 1 diabetes. *Diabetologia* 47:1940–1947, 2004
10. Harris ND, Heller SR: Sudden death in young patients with type 1 diabetes: a consequence of disease, treatment or both? *Diabet Med* 16:623–625, 1999
11. Campbell IW: Dead in bed syndrome: a new manifestation of nocturnal hypoglycaemia? *Diabet Med* 8:3–4, 1991
12. Weston PJ, Glancy JM, McNally PG, Thurston H, de Bono DP: Can abnormalities of ventricular repolarization identify insulin dependent diabetic patients at risk of sudden cardiac death. *Heart* 78:56–60, 1997
13. Heller SR: Abnormalities of the electrocardiogram during hypoglycemia: the cause of the dead in bed syndrome? *Int J Clin Pract Suppl* 129:27–32, 2002
14. Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D: The effect of acute hyperglycemia on QTc duration in healthy man. *Diabetologia* 43:571–575, 2000
15. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J: QT interval prolongation predicts cardiovascular mortality in an apparent healthy population. *Circulation* 84:1516–1523, 1991
16. Diabetes Research in Children Network (DIRECNET) Study Group: The accuracy of the CGMS in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) accuracy study. *Diabetes Technol Ther* 5:781–789, 2003
17. Eckert B, Agardh CD: Hypoglycemia leads to an increased QT interval in normal men. *Clin Physiology* 18:570–575, 1998
18. Cryer PE: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 27:2272–2279, 2004