Mechanisms of Abnormal Cardiac Repolarization During Insulin-Induced Hypoglycemia

Robert T.C.E. Robinson, Nigel D. Harris, Robert H. Ireland, Stuart Lee, Christopher Newman, and Simon R. Heller

Prolonged cardiac repolarization causes fatal cardiac arrhythmias. There is evidence that these contribute to sudden death associated with nocturnal hypoglycemia in young people with diabetes. We measured cardiac repolarization (QT interval [QTc] and QT dispersion [QTd]) during experimental hypoglycemia with and without β-blockade and potassium infusion to establish possible mechanisms. Two groups of 10 nondiabetic men (study 1 and study 2) each underwent four hyperinsulinemic clamps: two euglycemic (5 mmol/l) and two hypoglycemic (5 mmol/l and 2.5 mmol/l for 60 min each). Study 1 was performed with and without potassium infusion to maintain normal concentrations and study 2 with and without β-blockade (atenolol, 100 mg/day for 7 days). QTd was unchanged during euglycemia but increased during hypoglycemia (55 ms, $P < 0.0001$ vs. baseline), which was prevented by potassium (6 ms, $P = 0.78$). QTc increased significantly during hypoglycemia alone (67 ms, $P < 0.0001$) and during potassium replacement (46 ms, $P = 0.02$). In study 2, the increase in QTd during hypoglycemia (68 ms, $P < 0.0001$) was prevented by β-blockade (3 ms, $P = 0.88$). The increase in QTc during hypoglycemia (55 ms, $P < 0.0001$) was prevented by β-blockade (1 ms, $P = 0.98$). Our data indicate that hypoglycemia causes an acquired long QT syndrome. Sympathoadrenal stimulation is the main cause, through mechanisms that involve but are not limited to catecholamine-mediated hypokalemia. These abnormalities are prevented by selective β-blockade. *Diabetes* **52:1469–1474, 2003**

I n 1991, Tattersall and Gill (1) described a series of 22 deaths across the U.K. in young patients with type 1 diabetes and found strong circumstantial evidence that hypoglycemia had been the cause. The hallmark of the syndrome was unexpected death occurring during the night with the patient found lying dead in an undisturbed bed. The "dead in bed syndrome" has now been reported in other countries where it is possible to conduct detailed epidemiological surveys, notably in Scandinavia (2–4). Thordarson and Sovik (4) estimated that over 10 years, the overnight deaths of diabetic patients in which

hypoglycemia was implicated accounted for ~1 in 10 of all such deaths under the age of 40 years. Sudden overnight death was more common during the last 3 years of the study (1988–1990), which they related to the greater use of intensive insulin therapy. It appears to be significantly more frequent in those with diabetes compared with nondiabetic young individuals. Estimates are relatively crude, but Sartor and Dahlquist (3) reported an excess mortality rate 3–4 times that of the background population, with the greatest incidence seen in 15- to 19-year-olds.

We and others (5,6) have shown that moderate experimental hypoglycemia is associated with significant lengthening of the corrected QT interval (QTc) in subjects with and without diabetes (7). We observed a strong relationship between the increase in epinephrine and the increase in QTc and a weaker relationship between the decrease in plasma potassium and QT (5). We then showed a consistent increase in QTc during hypoglycemia in nondiabetic subjects and also recorded increased QT dispersion, another measure of cardiac repolarization (8).

This degree of abnormal repolarization has been associated with sudden death in other cardiac conditions caused by Torsade de Pointes ventricular tachycardia (VT). Congenital long QT syndrome is an inherited condition due to mutations in genes that code the voltage-gated ion channels responsible for the cardiac action potential (9,10). Affected individuals have a prolonged QTc and without treatment, a high risk of death due to VT (often precipitated by sympathoadrenal activation). Certain drugs (e.g., terfenadine and sotalol) also lengthen the QTc, and there is a relationship between the degree of lengthening and the chances of developing "Torsade de Pointes" VT (11).

We have proposed that these changes might contribute to the sudden death of young people with diabetes (12). If abnormal cardiac repolarization could contribute to sudden death in diabetes it is important to determine the pathophysiology, because this might lead to treatment to protect those at potential risk.

We hypothesized that two potential mechanisms might alter cardiac repolarization during hypoglycemia: *1*) a direct effect on the myocardium through sympathoadrenal activation, and *2*) hypokalemia caused by the stimulatory effects of both hyperinsulinemia and catecholamines on myocyte sodium potassium ATPase.

To establish their relative contributions we studied the effects of both β-adrenoceptor blockade and potassium replacement in separate experiments upon cardiac repo-

TABLE 1
The effect of potassium infusion on cardiac repolarization, measurements at baseline

	Euglycemia (− potassium)	Euglycemia (+ potassium)	Hypoglycemia (− potassium)	Hypoglycemia (+ potassium)	P
Glucose (mmol/l)	4.8 ± 0.07	4.6 ± 0.08	4.6 ± 0.14	4.8 ± 0.14	0.25
Insulin (mU/l)	8.4 ± 1.1	10.3 ± 3.8	7.4 ± 1.0	13.2 ± 4.6	0.57
Norepinephrine (nmol/l)	1.35 ± 0.19	1.11 ± 0.09	1.26 ± 0.16	1.07 ± 0.10	0.43
Heart rate (bpm)	62 ± 3	57 ± 3	55 ± 3	61 ± 4	0.051
Systolic BP (mmHg)	119 ± 2	118 ± 2	116 ± 2	114 ± 1	0.085
Diastolic BP (mmHg)	69 ± 2	69 ± 3	71 ± 2	67 ± 2	0.38

Data are means ± SE.

larization using hypoglycemic clamps in healthy nondiabetic subjects.

RESEARCH DESIGN AND METHODS

Subjects. We studied 19 nondiabetic male subjects: 10 completed a series of experiments involving potassium infusion (study 1), while a separate group of 10 underwent the experiments using β-blockade (study 2). One volunteer participated in both studies. All subjects had a normal resting electrocardiogram and none had symptoms of cardiovascular disease. Mean BMI and age (± SD) were 22.9 ± 2.7 kg/m^2 and 22.3 ± 2.6 years for study 1 and 22.3 ± 0.8 kg/m^2 and 20.8 ± 0.7 years for study 2. All subjects gave written consent to participate in this study, which was approved by the North Sheffield Local Research Ethics Committee.

Study design. In each study subjects underwent four hyperinsulinemic clamps (two euglycemic and two hypoglycemic) with each visit separated by at least 4 weeks. They were studied in the morning after an overnight fast. A cannula was placed in an antecubital vein of the nondominant arm for infusion of human soluble insulin (Actrapid; Novo Nordisk Laboratories, Copenhagen, Denmark) and glucose. A retrograde cannula for sampling was inserted in a dorsal hand vein of the nondominant arm with the hand kept in a heated box at 55°C to arterialize venous blood. Insulin was infused at a fixed rate (80 mU · m^{-2} · min^{-1}) and 20% (w/v) glucose solution (Baxter Healthcare, Thetford, Norfolk, U.K.) infused into the same vein. The infusion rate was adjusted every 5 min according to arterialized blood glucose measured at bedside using a glucose oxidase method (2300 M; Yellow Springs Instrument, Yellow Springs, OH).

All studies began with an equilibration infusion period of 40 min, during which blood glucose was maintained at 5 mmol/l. In the two euglycemic clamps, blood glucose was thereafter maintained at 5 mmol/l for a further 2 h. During the hypoglycemic clamps, however, blood glucose was held at 5 mmol/l during the 40-min equilibration period but then allowed to decrease over the following 60 min to 2.5 mmol/l, where it was maintained for a further 60 min. The end of the 40-min equilibration was designated time 0. Clamps were performed in random order with subjects blinded to their blood glucose. High-resolution electrocardiogram (EKG), 12-lead EKG, and blood samples (separated for later measurement of plasma insulin, potassium, epinephrine, and norepinephrine) were obtained at baseline (before the equilibration period), and at time 120 min (i.e., after 1 h of hypoglycemia and the equivalent time in the euglycemic clamps).

Study 1: potassium infusion study. In one euglycemic and one hypoglycemic clamp, subjects received a variable-rate potassium infusion (80 mmol/l in 0.9% [w/v] sodium chloride solution) to prevent the decrease in potassium associated with hyperinsulinemia plus or minus the increase in catecholamines/sympathoadrenal activation. The infusion rate was adjusted every 5 min according to whole blood potassium concentrations measured at the bedside, using an ion-specific electrode method (Bayer 654 Na/K Analyzer; Bayer Diagnostics, Berkshire, U.K.).

Study 2: β-adrenoceptor blockade study. To investigate the effect of β-adrenergic stimulation on ventricular repolarization, subjects were pretreated for 7 days with atenolol 100 mg daily, including the day of the study, before one euglycemic and one hypoglycemic clamp.

Measurement of QTc. EKGs were recorded on a custom built system for high-resolution EKG analysis that simultaneously acquires three bipolar orthogonal X, Y, and Z leads (5). Signals from sinus beats for each lead were amplified (15,000×), digitized (5 μV resolution at 750 samples/s.), filtered, and averaged on-line until the mean residual noise was <1.5 μV. An average of 10–30 beats at a rate of 1 every 6 s was required to achieve that figure. Only complexes with a correlation coefficient >99.5% were accepted in the average. The period of each measurement took ~6–7 min. The QTc was measured in the averaged X, Y, and Z signals individually. QTc was measured using a

tangent drawn at the point of maximal gradient on the downward slope of the T-wave and the end of the T-wave marked as the point of intersection of the tangent with the isoelectric line (13). The QTcs were marked using an on-screen cursor by two independent observers blinded both to the prevailing blood glucose and to the outcome of previous measurements and were calculated as the mean of the two measurements. The X, Y, and Z readings were then averaged to obtain an overall measure of the repolarization process.

Increases in heart rate are associated with a physiological reduction in the QTc. We corrected for differences in heart rate using the Bazett's formula to "normalize" the QTc to a heart rate of 60 beats/min (14) by dividing QT by the square root of the RR interval.

Measurement of QT dispersion. Twelve lead EKGs were recorded on a Burdick electrocardiograph at a paper speed of 50 mm/s and enlarged twofold before analysis. At least three complexes were measured in each lead. EKGs were analyzed manually in a blinded fashion. QTd was defined as the difference between the maximum and minimum QT across the 12 lead EKG (15). QTc on the 12 lead EKGs was measured from the beginning of the q-wave to the point at which the downward T-wave intersects the isoelectric line. In the presence of a U-wave, a tangent was drawn from the downward slope of the T-wave to the isoelectric line.

Metabolic measurements. Plasma epinephrine was analyzed by high-performance liquid chromatography with electrochemical detection (16). Total insulin was measured by radioimmunoassay using a double-antibody technique (17). Serum potassium was analyzed by direct potentiometry (Vitros Analyzer; Johnson and Johnson, Ortho Clinical Diagnostics, Haversham, Bucks, U.K.). The overall CVs were 0.60 and 0.63% for potassium concentrations of 4.2 and 7.5 mmol/l, respectively. Within-run CVs were 0.36, 0.22, and 0.47% for potassium concentrations of 2.52, 4.04, and 6.75 mmol/l, respectively.

Statistics. Results are expressed as means ± SE with 95% CIs. Baseline values between groups were compared using standard ANOVA methods. Values for baseline, 60, 90, and 120 min are shown in the Figures, but statistical analysis was limited to a comparison between values at 120 min (the time-point at which we observed the highest epinephrine and/or lowest potassium concentrations) and baseline. We used univariate ANCOVA with parameter estimates to assess the effect of potassium replacement and β-adrenoceptor blockade during euglycemia and hypoglycemia (18). This analysis adjusted for differences in baseline. Analyses were performed using SPSS for Windows (Version 10).

RESULTS

Study 1: the effect of potassium replacement on cardiac repolarization during hypoglycemia

Insulin and glucose. Insulin concentrations at baseline were similar in all four arms (P = 0.57) (Table 1). There was no difference in insulin concentrations achieved during insulin infusion (Table 2). Baseline glucose concentrations were similar in each arm (Table 1). Blood glucose concentrations were comparable during both the two euglycemic (P = 0.51) and hypoglycemic clamps (P = 0.94).

Potassium. Baseline potassium concentrations were comparable in all arms (P = 0.95). When potassium was infused during euglycemia and hypoglycemia (Fig. 1A), potassium concentrations remained within the normal range (3.5–4.5 mmol/l) but during euglycemia were 0.62

TABLE 2
The effect of potassium infusion on cardiac repolarization, measurements at 120 min

	Euglycemia (− potassium)	Euglycemia (+ potassium)	P	Hypoglycemia (− potassium)	Hypoglycemia (+ potassium)	P
Glucose (mmol/l)	4.8 ± 0.07	4.8 ± 0.08	0.51	2.5 ± 0.04	2.5 ± 0.02	0.94
Insulin (mU/l)	142.9 ± 9.8	149.3 ± 8.3	0.96	127.1 ± 9.6	123.2 ± 9.8	0.9
Norepinephrine (nmol/l)	1.44 ± 0.17	1.32 ± 0.14	0.45	1.57 ± 0.21	1.79 ± 0.20	0.58
Heart rate (bpm)	58 ± 3	58 ± 3	0.12	61 ± 3	68 ± 3	0.16
Systolic BP (mmHg)	120 ± 1	118 ± 1	0.69	122 ± 2	121 ± 3	0.68
Diastolic BP (mmHg)	66 ± 3	67 ± 2	0.57	58 ± 2	65 ± 2	0.1

Data are means ± SE.

mmol/l higher ([0.49, 0.74] $P < 0.0001$) with potassium infusion than without. Potassium concentrations during hypoglycemia were significantly greater with potassium then without (by 0.62 mmol/l [0.44, 0.79] $P < 0.0001$)

Catecholamines. Baseline plasma epinephrine across each of the four arms was similar ($P = 0.30$) (Fig. 1B). Epinephrine during euglycemia in the absence and presence of potassium was not significantly different (difference 0.17 nmol/l [−0.42, 0.75] $P = 0.56$). During hypoglycemia alone, epinephrine increased by 4.49 nmol/l ([3.93, 5.05] $P < 0.0001$) compared with euglycemia alone, and this was similar to the increase during hypoglycemia with potassium (4.66 nmol/l [3.85, 5.46] $P < 0.0001$). There was no significant difference in epinephrine during the two hypoglycemic arms (0.17 nmol/l [−0.64, 0.98] $P = 0.68$).

Baseline plasma norepinephrine concentrations were similar across each of the four arms ($P = 0.43$, Table 1). Norepinephrine during euglycemia in the absence and presence of potassium was not significantly different (0.132 nmol/l [−0.22, 0.48] $P = 0.45$).

During hypoglycemia alone, norepinephrine increased by 0.32 nmol/l ([−0.019, 0.66] $P = 0.063$) above euglycemia alone, and this was similar to the increase during hypoglycemia with potassium (0.45 nmol/l [−0.04, 0.94] $P = 0.08$). There was no significant difference in norepinephrine during the two hypoglycemic arms (0.13 [−0.36, 0.62] $P = 0.58$).

QTc. There was no difference in baseline QTc values in the four arms ($P = 0.44$) (Fig. 2A). QTc during euglycemia in the absence and presence of potassium was similar (dif-
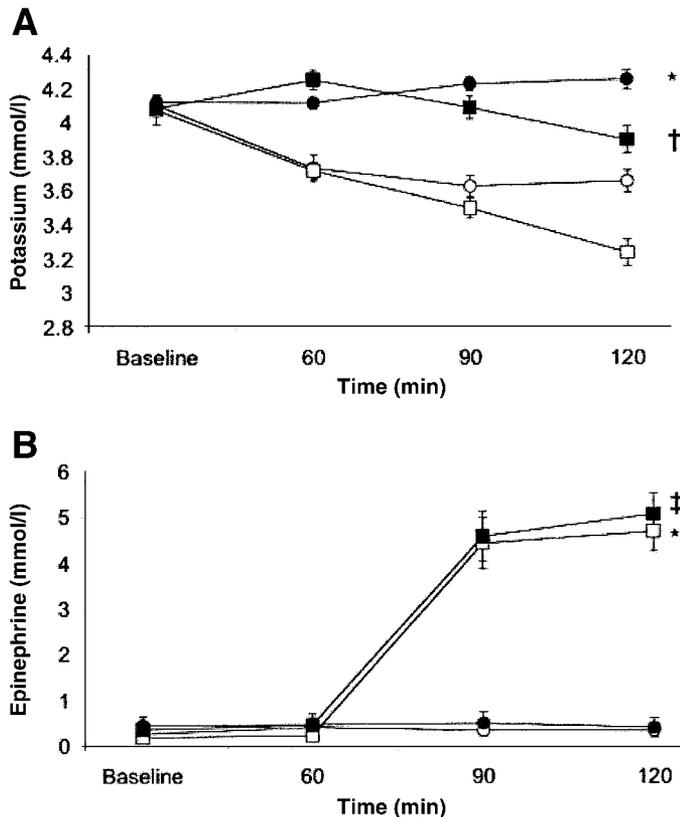

FIG. 1. Changes in potassium (A) and epinephrine (B) concentrations at baseline and over the last hour during euglycemia alone (○), euglycemia with potassium infusion (●), hypoglycemia alone (□), or hypoglycemia with potassium infusion (■). Results are expressed as means ± SE. *$P < 0.0001$ vs. euglycemia without potassium infusion; †$P < 0.0001$ vs. hypoglycemia without potassium infusion; ‡$P < 0.0001$ vs. euglycemia with potassium infusion.
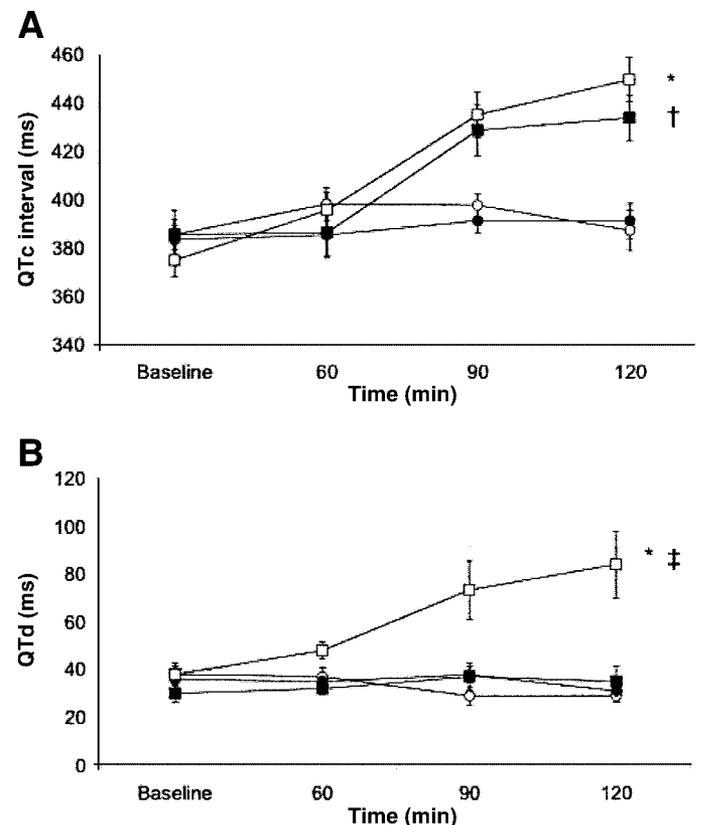

FIG. 2. Changes in QTc (A) and QTd (B) at baseline and over the last hour during euglycemia alone (○), euglycemia with potassium infusion (●), hypoglycemia alone (□), or hypoglycemia with potassium infusion (■). Results are expressed as means ± SE. *$P < 0.0001$ vs. euglycemia without potassium infusion; †$P < 0.05$ vs. euglycemia with potassium infusion; ‡$P < 0.05$ vs. hypoglycemia with potassium infusion.

TABLE 3
The effect of β-blockade on cardiac repolarization, measurements at baseline

	Euglycemia (− atenolol)	Euglycemia (+ atenolol)	Hypoglycemia (− atenolol)	Hypoglycemia (+ atenolol)	P
Glucose (mmol/l)	4.66 ± 0.21	4.66 ± 0.10	4.69 ± 0.17	4.58 ± 0.06	0.91
Insulin (mU/l)	9.7 ± 2.5	10 ± 2.4	11.9 ± 2.0	10.0 ± 2.1	0.17
Heart rate (bpm)	58 ± 3	49 ± 2	61 ± 3	51 ± 2	0.003
Systolic BP (mmHg)	118 ± 3	111 ± 2	125 ± 3	111 ± 4	0.0017
Diastolic BP (mmHg)	67 ± 2	64 ± 3	73 ± 2	65 ± 2	0.02

Data are means ± SE.

ference 5 ms [−12, 21] $P = 0.56$). During hypoglycemia alone, QTc increased by 67 ms ([50, 85] $P < 0.0001$) above that during euglycemia alone. During hypoglycemia with potassium, QTc increased by 46 ms ([13, 80] $P = 0.02$). The increases during both hypoglycemia arms were not significantly different (21 ms [−8, 50] $P = 0.16$).

QTd. There was a small but significant difference of 8 ms between the highest and lowest baseline values ($P = 0.012$) (Fig. 2B). When adjusted for baseline there was no significant change in QTd during or between either euglycemic arm (2 ms [−19, 23] $P = 0.85$). During hypoglycemia alone, QTd increased by 55 ms ([34, 76] $P < 0.0001$) above that during euglycemia alone. During hypoglycemia with potassium, QTd did not change significantly compared with euglycemia (6 ms [−37, 49] $P = 0.78$). There was a significantly greater increase in QTd during hypoglycemia alone compared with hypoglycemia with potassium by 49 ms ([11, 87] $P = 0.02$).

Pulse and blood pressure. Baseline heart rates during each of the four arms were similar, increasing to a similar extent during both hypoglycemic arms (Tables 1 and 2). There were minor differences in the change in systolic blood pressure (BP) from baseline during the two arms, but the increases during the two hypoglycemic arms were not significantly different. There were minor differences in the change in diastolic BP from baseline during the two arms, but the decreases during the two hypoglycemic arms were not significantly different.

Study 2: the effect of β-adrenoceptor blockade on cardiac repolarization during hypoglycemia

Insulin and glucose. Baseline insulin concentrations were similar in all four arms ($P = 0.17$ [ANOVA], Table 3) but reached significantly higher levels during infusion in the presence of β-blockade. Baseline glucose concentrations were similar in each arm (Table 3). Blood glucose concentrations were comparable during the two euglycemic ($P = 0.29$) and hypoglycemic clamps (0.98) (Table 4).

Potassium. Baseline potassium concentrations were comparable in all arms ($P = 0.16$) (Fig. 3). During eugly-

cemia with and without β-blockade there was no difference in potassium (0.05 mmol/l [−0.09, 0.19] $P = 0.46$). During hypoglycemia without β-blockade, potassium decreased significantly (by −0.4 mmol/l [−0.54, −0.26] $P < 0.0001$) below euglycemia alone, while after β-blockade the decrease was not significant (−0.16 mmol/l [−0.44, 0.12] $P = 0.26$). The concentrations reached during the two hypoglycemic arms were not significantly different (0.24 mmol/l [−0.01, 0.48] $P = 0.06$).

Catecholamines. Baseline epinephrine and norepinephrine concentrations were similar in each arm. Because circulating concentrations are modified by the presence of β-blockade (19) and circulating levels are not related to biological activity, these are not presented in detail.

QTc. Baseline QTc values were significantly lower in atenolol-treated subjects ($P = 0.0003$) (Fig. 4A). When adjusted for baseline, there was no difference in the increase in QTc during euglycemia with and without β-blockade (19 ms [51, −13] $P = 0.23$). During hypoglycemia alone QTc increased by 55 ms ([29, 80] $P < 0.0001$) above euglycemia alone but not significantly (1 ms [−53, 55] $P = 0.98$) during hypoglycemia with β-blockade. There was a significant difference in Δ-QTc between both hypoglycemic arms of 54 ms ([6, 102] $P = 0.04$).

QTd. Baseline QTd intervals were similar in each arm ($P = 0.14$) (Fig. 4B). When adjusted for baseline there was no significant change in QTd during or between either euglycemic arm (−1 ms [−21, 18] $P = 0.88$). During hypoglycemia alone QTd increased by 68 ms ([47, 89] $P < 0.0001$) above euglycemia alone but not significantly (3 ms [−37, 43] $P = 0.88$) during hypoglycemia with β-blockade. There was a significant difference in Δ-QTd between both hypoglycemic arms of 65 ms ([31, 96] $P < 0.0001$).

Pulse and BP. Heart rates were significantly lower in the atenolol arms at baseline and during hypoglycemia (Tables 3 and 4). Systolic and diastolic BP were significantly lower in the atenolol arms at baseline and during eu- and hypoglycemia. During hypoglycemia alone, systolic BP was unchanged compared with euglycemia (2 mmHg [−4,

TABLE 4
The effect of β-blockade on cardiac repolarization, measurements at 120 min

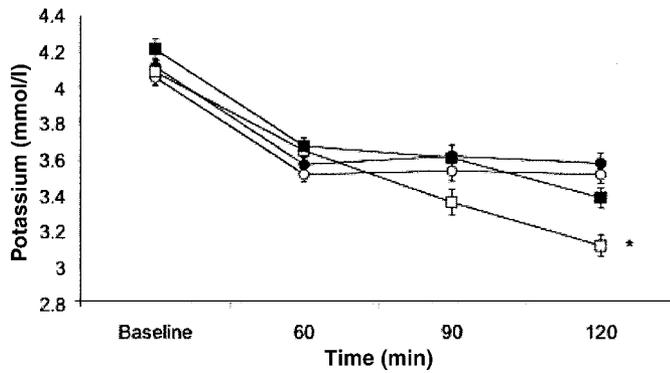|	Euglycemia (− atenolol)	Euglycemia (+ atenolol)	P	Hypoglycemia (− atenolol)	Hypoglycemia (+ atenolol)	P
Glucose (mmol/l)	5.0 ± 0.02	5.0 ± 0.02	0.29	2.5 ± 0.02	2.5 ± 0.02	0.98
Insulin (mU/l)	145 ± 7.4	156.6 ± 8.9	0.02	129 ± 9.6	156 ± 12.1	0.001
Heart rate (bpm)	56 ± 2	50 ± 2	0.046	67 ± 3	51 ± 2	0.009
Systolic BP (mmHg)	127 ± 2	112 ± 2	0.0001	133 ± 4	111 ± 4	0.0001
Diastolic BP (mmHg)	73 ± 2	63 ± 1	0.001	65 ± 2	59 ± 2	0.001

Data are means ± SE.

FIG. 3. Changes in potassium concentration at baseline and over the last hour during euglycemia alone (○), euglycemia with atenolol (●), hypoglycemia alone (□), or hypoglycemia with atenolol (■). Results are expressed as means ± SE. *$P < 0.0001$ vs. euglycemia without atenolol.

FIG. 4. Changes in QTc (*A*) and QTd (*B*) at baseline and over the last hour during euglycemia alone (○), euglycemia with atenolol (●), hypoglycemia alone (□), or hypoglycemia with atenolol (■). Results are expressed as means ± SE. *$P < 0.0001$ vs. euglycemia without atenolol; †$P < 0.05$, ‡$P < 0.0001$ vs. hypoglycemia with atenolol.

8] $P = 0.66$), and diastolic BP was 6 mmHg lower ([−10, −3] $P = 0.002$). Systolic and diastolic pressures did not change during those arms where subjects were under β-blockade.

DISCUSSION

These data confirm that acute experimental hypoglycemia leads to abnormal cardiac repolarization with an increase of QTc and QTd from baseline of ~75 and 55 ms, respectively. Such an increase is sufficient in some clinical conditions to produce serious cardiac arrhythmias (20–24). We have also shown that the increase in QTd during hypoglycemia was completely prevented by both potassium replacement and β-adrenoceptor blockade but that the increase in QTc was reduced only by β-blockade. During hyperinsulinemic-euglycemia, potassium decreased within the normal range [presumably due to insulin-stimulated activation of Na/K ATPase (25,26) since catecholamine levels remained low], but QTd and QTc did not change significantly. The data therefore also indicate that *1*) decreases in plasma potassium induced during hyperinsulinemic clamps are not sufficient to affect cardiac repolarization at euglycemic levels and *2*) sympathoadrenal activation is largely responsible for abnormal cardiac repolarization during hypoglycemia. The finding that potassium infusion prevented QTd during hypoglycemia suggests that hypoglycemia-induced abnormalities in cardiac repolarization are in part a result of sympathetically mediated decreases in circulating potassium. However, because β-adrenergic blockade prevented both hypoglycemia-induced QTc and QTd lengthening despite a decrease in plasma potassium, the sympathoadrenal system also appears to have a direct effect on the myocardium.

Cardiac repolarization returns the positive membrane potential at the end of depolarization back to its negative resting state, and its duration is conventionally measured by QTc (27,28). A prolonged QTc increases the susceptibility of the myocardium to re-entry VT, possibly triggered by spontaneous mini-depolarizations as the cell repolarizes (28).

QT prolongation can be induced by either a decrease in outward repolarizing currents, mainly carried by potassium ions, or an increase in inward (depolarizing) current, carried by sodium or calcium ions (29). In the congen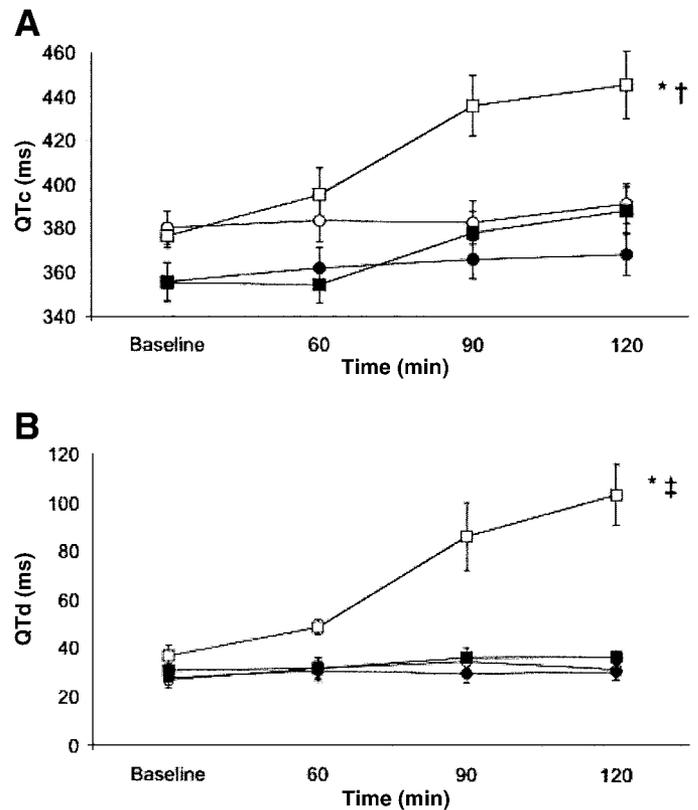ital long QT syndrome, alterations in these currents are produced by mutations in the genes encoding the different ion channel proteins (10,30). Our data indicate that insulin-induced hypoglycemia causes an acquired form of long QT syndrome, possibly through a direct effect of epinephrine, which regulates potassium (31), calcium (32), and chloride channels (33) via increases in cAMP.

Our finding that QTc and QTd responded differently to potassium and sympathetic blockade during hypoglycemia suggests that the mechanisms underlying these two indicators of cardiac repolarization may be different, and there is other evidence that they represent different aspects of cardiac electrophysiology (34,35). The changes in QTd indicate that hypoglycemia increases the heterogeneity of cardiac repolarization, arguably the main factor in determining dysrhythmia risk. Furthermore, the effect of atenolol, which prevented the increase in both QTc and QTd highlights a possible therapeutic approach if it proves possible to identify those at greatest potential risk.

Our experimental model of hypoglycemia demonstrated substantial changes in the EKG during hypoglycemia but has important potential limitations in reflecting the clinical situation. Insulin concentrations during hyperinsulinemic glucose clamps are higher than those seen during subcutaneous therapy in those with diabetes. Furthermore, many patients, particularly those with a long duration of disease or tight glycemic control have a diminished adrenaline response during hypoglycemia (36,37), particularly when asleep (38). Thus, decreases in serum potassium and sympathetic activation are less pronounced during clinical

episodes of hypoglycemia. Nevertheless, some patients experience marked autonomic responses during severe hypoglycemia that could both lower serum potassium and alter cardiac repolarization. It seems worthwhile exploring the alterations in plasma potassium and recording the EKG during clinical episodes of hypoglycemia particularly, at night.

In summary, we have shown that prolonged cardiac repolarization produced by hypoglycemia is a consequence of sympathoadrenal stimulation acting both directly on the myocardium and through decreases in potassium. We have also demonstrated that selective β-blockade can prevent these effects in normal subjects. If it proves possible to identify patients with type 1 diabetes who are at particular risk of severely prolonged QT lengthening during hypoglycemia, these agents might have a therapeutic role.

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