ORIGINAL ARTICLES

Electrocardiographic Alterations during Hyperinsulinemic Hypoglycemia in Healthy Subjects

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Background: We evaluated the arrhythmogenic potential of hypoglycemia by studying electrocardiographic (ECG) changes in response to hyperinsulinemic hypoglycemia and associated sympathoadrenal counterregulatory responses in healthy subjects.

Methods: The study population consisted of 18 subjects, aged 30–40 years. Five-minute ECG recordings and blood samplings were performed at baseline and during the euglycemic and hypoglycemic hyperinsulinemic clamp studies. PR, QT, and QTc intervals of electrocardiogram and ECG morphology were assessed from signal-averaged ECG.

Results: Although cardiac beat interval remained unchanged, PR interval decreased ($P < 0.01$) and QTc interval ($P < 0.001$) increased in response to hyperinsulinemic hypoglycemia. Concomitant morphological alterations consisted of slight increases in R-wave amplitude and area ($P < 0.01$ for both), significant decreases in T-wave amplitude and area ($P < 0.001$ for both), and moderate ST depression ($P < 0.001$). Counterregulatory norepinephrine response correlated with amplification of the R wave ($r = -0.620$, $P < 0.05$) and epinephrine response correlated with flattening of the T wave ($r = -0.508$, $P < 0.05$).

Conclusions: Hyperinsulinemic hypoglycemia with consequent sympathetic humoral activation is associated with several ECG alterations in atrioventricular conduction, ventricular depolarization, and ventricular repolarization. Such alterations in cardiac electrical function may be of importance in provoking severe arrhythmias and “dead-in-bed” syndrome in diabetic patients with unrecognized hypoglycemic episodes.

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ECG; epinephrine; hypoglycemia; insulin; norepinephrine

Hypoglycemia has been suggested to trigger arrhythmic events and myocardial ischemia in diabetic patients by mechanisms related to exaggerated sympathetic activation and increased catecholamine secretion.^{1–3} Sympathoadrenal counterregulation results in increased plasma epinephrine concentration, systemic norepinephrine spillover, as well as plasma norepinephrine concentration, and concomitant hyperinsulinemia seems to cause further increase in sympathetic activation.^{4–6} We have previously demonstrated a remarkable increase in plasma epinephrine concentration without parallel changes in vagally mediated heart rate

variability during hyperinsulinemic hypoglycemia, which reflects a change in the sympathovagal balance toward sympathetic predominance.⁷ This observation is of importance because a relative hyperadrenergic tone is suspected to play a role in the mechanisms behind sudden cardiac death.

The underlying connecting mechanisms in hypoglycemia-associated sympathoadrenal activation and its arrhythmogenic consequences are still unclear. Hypoglycemia changes the ventricular repolarization, which is thought to be caused by either a sympathoadrenal stimulation^{8–10} or change in potassium level.^{11,12} There is evidence

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to suggest that epinephrine has direct effect upon the myocardium that prolongs the QTc interval^{13,14} and flattens the T wave.¹³ Such epinephrine-induced changes can be prevented by labetalol, an alpha- and beta-blocker.¹³ In line with this, T-wave and QTc changes during experimental hypoglycemia have been found to become blunted after the administration of beta-blocking agents.^{10,15} Although the impact of increased epinephrine level on ventricular repolarization during hypoglycemia has been previously evaluated, less attention has been paid to the role of norepinephrine response. Furthermore, previous studies have mainly focused on changes in the duration of ventricular repolarization and amplitude of the T wave, while other electrocardiographic (ECG) changes during hypoglycemia are largely unknown.

Based on the notion that counterregulatory sympathoadrenal activation is the primary mechanism behind cardiac electrophysiological changes and electrical instability,⁸ we hypothesized that catecholamine responses during hypoglycemia are closely associated with myocardial electrophysiological changes. Therefore, we investigated the relationship between sympathoadrenal counterregulatory and ECG responses to acute hyperinsulinemia and hypoglycemia in healthy subjects by assessing changes in sympathetic hormonal regulation and concomitant changes in ECG morphology and time intervals related to atrioventricular conduction and ventricular repolarization during the euglycemic and hypoglycemic hyperinsulinemic clamp studies.

METHODS

Subjects

The study population has been described in detail.^{7,16} The subjects for the present study were 18 healthy subjects who had to fulfill the following criteria: (1) age between 30 and 40 years, (2) no impaired glucose regulation, (3) no first-degree relatives with a history of diabetes, (4) no drug treatment nor any disease that could potentially modify carbohydrate metabolism, and (5) no strenuous physical activity more than three times per week. Eight subjects were the parents of patients with congenital hyperinsulinemia who were homozygous for the sulfonylurea receptor-1 (SUR1) mutation. All of them had appropriate insulin secretion, normal glucose tolerance, insulin sensitivity,

counterregulatory system function, and cardiovascular autonomic regulation as reported earlier.^{7,16}

Study Protocol

The study protocol was approved by the ethics committee of Kuopio University Hospital. Informed consent was given by all subjects. The subjects were admitted to the metabolic ward of the department of medicine, Kuopio University Hospital, where the intravenous (IV) glucose tolerance test was performed followed by the hyperinsulinemic euglycemic and hypoglycemic clamp studies.

Procedures

Subjects were placed in the supine position and instrumented for the ECG recordings. Intravenous catheters were placed in the right and left antecubital fossae for insulin/glucose infusion and for obtaining blood for glucose and hormonal analyses.

Euglycemic and Hypoglycemic Clamps

The degree of insulin resistance was evaluated with the euglycemic hyperinsulinemic clamp technique.¹⁷ A priming dose of IV insulin infusion (Actrapid 100 IU/mL, Novo Nordisk, Gentofte, Denmark) was administered during the initial 10 minutes to acutely raise plasma insulin to the desired level, where it was maintained by a continuous IV insulin infusion at a rate of 80 mU/m² body surface area/minute. Blood glucose was clamped at 5.0 mmol/L for the next 120 minutes (the euglycemic clamp 0–120 minutes) and then at 3.0 mmol/L for the next 120 minutes (the hypoglycemic clamp 120–240 minutes) by infusing intravenously 20% glucose at varying rates according to blood glucose measurements performed at 5-minute intervals (mean coefficient of variation of blood glucose <3% during the euglycemic clamp and 3% during the hypoglycemic clamp). Steady-state phase was defined as the period when blood glucose was maintained at a desired level by a constant glucose infusion. The rates of whole-body glucose uptake (M value) were measured according to the mean value for the period from 60 to 120 minutes during the euglycemic clamp and hypoglycemic clamp.

Blood Sampling

The blood samples for the measurement of plasma insulin, plasma epinephrine, and plasma norepinephrine were drawn at baseline, at 90 minutes during the euglycemic clamp (normoglycemic state) and again during hypoglycemia at 240 minutes during the hypoglycemic clamp.

Assays and Calculations

Blood glucose was measured with the glucose oxidase method (Glucose & Lactate Analyzer 2300 Stat Plus; Yellow Springs Instrument Co., Inc., Yellow Springs, OH). For the determination of plasma insulin, blood was collected into ethylenediaminetetraacetic acid (EDTA) tubes. After centrifugation, the plasma for the determination of insulin was stored at -20°C until analysis. Plasma insulin was determined by radioimmunoassay (Phadeseph Insulin RIA 100; Pharmacia Diagnostics AB, Uppsala, Sweden). Insulin assay also detected proinsulin and proinsulin conversion products, with a crossreactivity of 47%. The counterregulatory epinephrine and norepinephrine responses were analyzed by high-performance liquid chromatography with electrochemical detection (plasma catecholamine reagent kit and column from Chromsystems GmbH, Munich, Germany).

Recordings

Electrodes were placed for modified chest lead 5 (V_5) ECG recording. Five-minute electrocardiogram signals were recorded in the supine position at baseline and during the steady state of the euglycemic hyperinsulinemic clamp and the hypoglycemic hyperinsulinemic clamp. During the recordings, subjects were in the supine position and were asked to breathe according to a metronome at 0.2-Hz frequency with their normal tidal volume. Recorded signals were analogue-to-digital converted with temporal resolution of 200 Hz/channel and amplitude resolution of 12 bits. Data acquisition was performed with an IBM/PC-compatible microcomputer with CAFTS software (Medikro Ltd., Kuopio, Finland).

Signal-Averaged ECG Analyses

Stationary data sets of 100 seconds free of technical artifacts and ectopic beats were selected for analyses during each phase. From the signal-averaged ECG, PR interval was analyzed by de-

tecting the time interval between the local maximum of the P wave and R peak. The end of the T wave was determined as a crossing point of the tangent (positioned on the half-amplitude of the T wave) on the descending portion of the T wave and isoelectric line. The QT interval was determined as the time elapsed from the onset of the Q wave to the end of the T wave. To assess reproducibility of QT-interval analysis, all recordings were analyzed twice by the same observer and also once by an independent observer. Coefficients of variation for intraobserver variability for QT interval were 1.7% in baseline recordings, 1.7% in the euglycemic clamp, and 1.5% in the hypoglycemic clamp. Corresponding between-observer coefficients of variation were 1.7%, 2.0%, and 2.0%. The corrected QT interval (QTc interval) was computed according to the Bazett formula ($\text{QTc-Bazett} = \text{QT}/\text{RR interval}^{1/2}$), the Fridericia formula ($\text{QTc-Fridericia} = \text{QT}/\text{R-R interval}^{1/3}$), and by the Karjalainen nomogram method (QTc-Karjalainen). Although the source of error related to different methods for correction for cardiac cycle length seems to be marginal in clinical practice, with heart rates close to normal, possible under- and overcorrection of the QTc interval depending on heart rate may result in statistical significance in population-based studies with evaluation of dynamic aspects of QTc-interval behavior. We decided to use in further statistical analyses QTc-Karjalainen, which is known to provide accurately adjusted values of QT in different heart rates. Amplitudes and areas of the R and T waves were measured. ST deviation from the isoelectric line was assessed as position shift 60 ms after the end of QRS complex. Data analyses were performed with an IBM/PC-compatible microcomputer with WINCPRS software (Absolute Aliens Oy, Turku, Finland)¹⁸ and reliability of automated data analyses was controlled by visual evaluation of the ECG signal.

Statistical Analysis

Because hormone levels were not normally distributed, the data were analyzed using nonparametric tests. Friedman's test over three-point time trends was performed on ECG and hormone parameters. If statistically significant ($P < 0.05$), the Wilcoxon's matched-pairs signed-rank test was applied to define further the effects of hyperinsulinemia and hypoglycemia. Univariate correlations were analyzed by Spearman's rank correlation analysis. Calculations were performed with the

Table 1. Clinical and Biochemical Characteristics (Mean $\pm$ SEM)

n	18
Age (years)	35 $\pm$ 1
Sex (male/female)	9/9
Systolic blood pressure (mmHg)	128 $\pm$ 3
Diastolic blood pressure (mmHg)	81 $\pm$ 2
Body mass index (kg/m ²)	23.5 $\pm$ 0.6
Fasting blood glucose (mmol/L)	4.5 $\pm$ 0.1
Fasting plasma insulin (pmol/L)	45.9 $\pm$ 4.3
Whole-body glucose uptake during	
Euglycemic clamp (μ mol/kg/min)	63.1 $\pm$ 3.2
Hypoglycemic clamp (μ mol/kg/min)	46.3 $\pm$ 2.5

SEM = standard error of the mean.

SPSS for Windows software (SPSS, Inc., Chicago, IL). Data are shown as the mean $\pm$ SEM.

RESULTS

Clinical and biochemical characteristics of subjects are shown in Table 1.

Euglycemic or hypoglycemic hyperinsulinemia was not associated with statistically significant

changes in cardiac beat interval (RR interval). However, time-related (baseline – euglycemic hyperinsulinemia – hypoglycemic hyperinsulinemia) changes were observed in PR interval ($P < 0.01$), R-wave amplitude and area ($P < 0.01$ for both), ST level ($P < 0.001$), T-wave amplitude and area ($P < 0.001$ for both), as well as in QTc interval ($P < 0.001$) (Fig. 1, Table 2). Concomitantly, plasma epinephrine ($P < 0.001$) and norepinephrine ($P < 0.05$) concentrations increased during the protocol.

During euglycemic hyperinsulinemia, no statistically significant changes were found in RR, PR, and QT intervals and plasma catecholamine concentrations (Table 2). However, we observed a modest increase in R-wave amplitude and area ($P < 0.05$ for both) and QTc interval ($P < 0.01$) in response to euglycemic hypoglycemia. Furthermore, T-wave amplitude ($P < 0.001$), T-wave area ($P < 0.01$), and ST segment ($P < 0.01$) decreased during the euglycemic hyperinsulinemic clamp compared to baseline measurements.

In response to hyperinsulinemic hypoglycemia, we observed a shortening of the PR interval (P-value: vs baseline <0.05 and vs euglycemic hyperinsulinemia <0.01), further depression of the ST

Figure 1. A representative case showing a slight amplification of the R wave, a decrease in the ST segment, a remarkable flattening of the T wave, and a slight prolongation of the QT interval as characteristic electrocardiographic changes in response to euglycemic and hypoglycemic hyperinsulinemia.

Table 2. Electrocardiographic Parameters and Plasma Catecholamine Concentrations during the Euglycemic and Hyperglycemic Clamp Studies (Mean $\pm$ SEM)

	Baseline	Euglycemia	Hypoglycemia	P Value
RR interval (ms)	904 $\pm$ 31	886 $\pm$ 26	857 $\pm$ 31	0.211
PR interval (ms)	154 $\pm$ 8	155 $\pm$ 8 ^{‡‡}	147 $\pm$ 7 [†]	0.007
R-wave amplitude (mV)	2.96 $\pm$ 0.25*	3.02 $\pm$ 0.24	3.03 $\pm$ 0.24 [†]	0.006
R-wave area (mV $\times$ s)	0.074 $\pm$ 0.007*	0.077 $\pm$ 0.007	0.078 $\pm$ 0.008 [†]	0.004
ST deviation (mV)	-0.08 $\pm$ 0.03**	-0.13 $\pm$ 0.03 ^{‡‡}	-0.16 $\pm$ 0.03 ^{†††}	<0.001
T-wave amplitude (mV)	0.55 $\pm$ 0.08***	0.30 $\pm$ 0.06 ^{‡‡‡}	0.20 $\pm$ 0.05 ^{†††}	<0.001
T-wave area (mV $\times$ s)	0.048 $\pm$ 0.009***	0.030 $\pm$ 0.006 ^{‡‡‡}	0.017 $\pm$ 0.006 ^{†††}	<0.001
QT interval (ms)	378 $\pm$ 7	384 $\pm$ 6	395 $\pm$ 8	0.103
QTc-Bazett (ms)	399 $\pm$ 4**	408 $\pm$ 5 ^{‡‡}	429 $\pm$ 7 ^{††}	<0.001
QTc-Fridericia (ms)	392 $\pm$ 4**	399 $\pm$ 5 ^{‡‡}	417 $\pm$ 6 ^{††}	<0.001
QTc-Karjalainen (ms)	393 $\pm$ 4**	400 $\pm$ 4 ^{‡‡}	417 $\pm$ 6 ^{††}	<0.001
Epinephrine (nmol/L)	0.18 $\pm$ 0.03	0.20 $\pm$ 0.03 ^{‡‡‡}	1.68 $\pm$ 0.32 ^{†††}	<0.001
Norepinephrine (nmol/L)	1.74 $\pm$ 0.22	1.63 $\pm$ 0.18 ^{‡‡}	2.02 $\pm$ 0.19 [†]	0.025

Significances: NS = nonsignificant, *P < 0.05 between baseline and euglycemia, **P < 0.01 between baseline and euglycemia, ***P < 0.001 between baseline and euglycemia, [†]P < 0.05 between baseline and hypoglycemia, ^{††}P < 0.01 between baseline and hypoglycemia, ^{†††}P < 0.001 between baseline and hypoglycemia, [‡]P < 0.05 between euglycemia and hypoglycemia, ^{‡‡}P < 0.01 between euglycemia and hypoglycemia, ^{‡‡‡}P < 0.001 between euglycemia and hypoglycemia.

segment (P-value: vs baseline <0.01 and vs euglycemic hyperinsulinemia <0.05), flattening of the T wave (P-value: vs baseline <0.001 and vs euglycemic hyperinsulinemia <0.01), and decrease in the T-wave area (P-value: vs baseline <0.001 and vs euglycemic hyperinsulinemia <0.001) (Table 2). We also found a prolongation in QTc interval (P-value: vs baseline <0.01 and vs euglycemic hyperinsulinemia <0.01) in response to hyperinsulinemic hypoglycemia. Catecholamine levels increased significantly when comparing hypoglycemia with baseline or euglycemia (Table 2).

Counterregulatory epinephrine response was associated with the flattening of the T wave and norepinephrine response with the change in the R-wave amplitude (Table 3, Fig. 2). Other ECG changes were not significantly correlated with catecholamine responses.

All statistical analyses were also carried out by comparing carriers and noncarriers of the V187D mutation. No differences in any of the parameters measured were found.

DISCUSSION

The main finding of this study is that hyperinsulinemic hypoglycemia was associated with several ECG alterations indicating changes in atrioventricular conduction, ventricular depolarization, and ventricular repolarization. Hyperinsulinemia per

se seems to modulate amplitudes of the R and T waves, ST deviation, and the duration of the QTc interval.

Hypoglycemia has marked effects on the cardiac electrical function because it markedly potentiates the effects of hyperinsulinemia on ST deviation, T wave, and QTc interval, and it also seems to be responsible for the changes in the PR interval. Our results also suggest that counterregulatory adrenergic activation is linked with morphological changes in T waves. This observation supports the concept of sympathoadrenal response as an underlying cause

Table 3. Univariate Correlations between Counterregulatory Catecholamine Responses and Changes in ECG Variables during the Hyperinsulinemic Hypoglycemic Clamp

Variable	Counterregulatory Response	
	Δ Epinephrine	Δ Norepinephrine
Δ RR interval	-0.221	-0.247
Δ PR interval	0.263	0.221
Δ QT interval	-0.050	-0.206
Δ QTc interval	0.194	-0.037
Δ R-wave amplitude	-0.108	-0.620*
Δ R-wave area	-0.256	-0.434
Δ T-wave amplitude	-0.508*	-0.237
Δ T-wave area	-0.373	-0.118
Δ ST deviation	-0.306	-0.256

Values are Spearman's correlation coefficients. *P < 0.05.

Figure 2. Relationships between (A) counterregulatory norepinephrine response and a change in the amplitude of the R wave and (B) counterregulatory epinephrine response and a change in the amplitude of the T wave during hyperinsulinemic hypoglycemia. Values represent changes between hypoglycemia and baseline.

for changes in ventricular repolarization during hypoglycemia. On the other hand, shortening of the PR interval, depression of the ST segment, and prolongation of the QTc intervals did not correlate with catecholamine responses, indicating that some other mechanisms may be of importance as well.

PR interval remained practically unchanged during the euglycemic hyperinsulinemic clamp, which is in line with a previous report showing that in subjects with normal atrioventricular conduction, glucose-insulin-potassium infusion had no influence on the atrioventricular conduction time.¹⁹ However, there is some evidence suggesting that an increase in extracellular glucose or glucose-insulin-potassium infusion could restore depressed atrioventricular nodal electrical activity.^{19,20} Less is known about the effect of hypoglycemia on atrioventricular nodal function. Cardiac sympathetic stimulation inhibits vagal action on atrioventricular conduction for prolonged periods.²¹ Thus, observed PR-interval shortening during the hypoglycemic clamp can be considered as an expected response that is likely to be related to counterregulatory adrenergic stimulation and consequent acceleration of atrioventricular conduction.

In the present study, we found an association between the change in the R-wave morphology and counterregulatory norepinephrine response. First, in response to euglycemic hyperinsulinemia, the

amplitude and area of the R wave increased, while plasma epinephrine concentration was unchanged. In the hypoglycemic phase, norepinephrine level started to increase without further changes in the R-wave morphology. Second, the correlation between the amplification of the R wave and the increase in plasma norepinephrine concentration was negative, suggesting that the effect of euglycemic hyperinsulinemia on R-wave amplification was impaired in subjects with larger sympathoadrenal counterregulatory response. Taken together, R-wave changes seem to be associated with norepinephrine response, but are not directly caused by counterregulatory sympathetic action.

We found that both hyperinsulinemia and hypoglycemia induced a slight but statistically significant ST-segment decrease in healthy subjects. Because none of our healthy subjects experienced chest pain, the mechanisms behind ST deviation are likely to be nonischemic. However, it is not possible to exclude silent myocardial ischemia without the assessment of myocardial metabolic function. This is particularly the case in diabetic patients in whom hypoglycemia has been suggested to induce myocardial ischemia.^{2,22–24}

T-wave flattening is one of the most characteristic findings during hypoglycemia.^{11,25,26} Such response is so evident and reproducible that R wave-to-T wave ratio has been considered to be a

possible indicator of hypoglycemia in ECG-based hypoglycemia detection technique.²⁵ Decreases in T-wave amplitude and area were evident during hyperinsulinemic hypoglycemia, but pronounced T-wave flattening occurred also during euglycemic hyperinsulinemia. Thus, T-wave changes seem to be modulated by different kind of factors related to glucose regulation. Our observation of a strong association between the decrease in the T-wave amplitude and the increase in plasma epinephrine concentration supports the concept of sympathoadrenal response as an important cause for changes in the ventricular repolarization during hypoglycemia. Previous studies have demonstrated that acute hyperinsulinemia causes sympathetic activation.^{27,28} Thus, similar mechanisms could explain T-wave changes in both euglycemic and hypoglycemic hyperinsulinemia. In the latter case, pronounced response could be produced by further activation of the sympathoadrenal counterregulation.

We found that QTc interval increased during euglycemic hyperinsulinemia and, especially, during hypoglycemia. This is in agreement with previous studies evaluating the QTc response during moderate experimental hyperinsulinemia^{29,30} or during hypoglycemia.^{11,26,31} Because prolonged cardiac repolarization causes cardiac arrhythmias and may contribute to sudden death, it has been suggested that the QTc prolongation during nocturnal hypoglycemia is of clinical importance.⁸ Based on the hypothesis that sympathoadrenal stimulation and hypokalemia are potential causes of hypoglycemia-induced alteration in cardiac repolarization, Robinson and coworkers studied the effects of beta-adrenoreceptor blockade and potassium replacement.⁸ They found that the QTc prolongation in response to experimental hypoglycemia could be prevented by beta-blockade, but not by potassium replacement. Their results suggest that sympathoadrenal stimulation is the main cause through mechanisms that are not limited to catecholamine-mediated hypokalemia. On the other hand, in children and adolescents with type 1 diabetes, the QTc prolongation related to nocturnal hypoglycemia has been found to occur irrespective of changes in epinephrine level.¹² Thus, it is likely that in subjects with recurrent hypoglycemic episodes, mechanisms other than epinephrine stimulation are also involved in QTc prolongation. In our study, QT- and QTc-interval responses did not significantly correlate with catecholamine re-

sponses. However, risk of type II error cannot be entirely excluded.

Our study population consisted of 18 healthy men and women aged 30–40 years. Eight of them were carriers of an inactivating beta-cell ATP-sensitive K(+) channel mutation, but they had normal glucose tolerance and insulin sensitivity and appropriate insulin secretion,¹⁶ as well as normal hemodynamic and cardiovascular autonomic responses to hypoglycemia,⁷ which justifies their inclusion to this study. Furthermore, no differences in any parameters measured were found between carriers of the V187D mutation compared to non-carriers. Although there is a well-known problem with the difficulty of measuring the QT interval, especially during hypoglycemia, when the T wave is flattened and end of the T wave may be quite indistinct, our controlled computerized method was found to be very reproducible. Even during the hypoglycemic clamp, coefficients of variation were 1.5% and 2.0% for intraobserver and interobserver variability, respectively. Therefore, we think that the source of bias related to problem of relative inaccuracy and unreliability of the QT measurement may not play a significant role in our study. With regard to QT correction methods, we confirmed previous finding of artificial prolongation of the QTc-Bazett compared to QTc-Fridericia and QTc-Karjalainen when RR interval was <1.0 second. Therefore, a more detailed evaluation of dynamic changes in QTc interval was done according to QTc-Karjalainen because it is thought to provide most accurately the adjusted values of QT in different heart rates.

There are some limitations in our study that reduce the possibility to evaluate the mechanisms behind observed ECG changes or the possibility to evaluate possible alterations in relation to diabetic process. First, we measured sympathetic counterregulatory response by the assessment of catecholamine concentrations in plasma that do not reflect direct sympathetic activity in heart. Catecholamine levels in plasma reflect general sympathetic hormonal regulation, but not regional neural outflow to specific organs. Second, because plasma potassium concentrations were not measured, we cannot evaluate the effect of hypokalemia caused by hyperinsulinemia and catecholamine stimulation. Furthermore, responses were measured during the hyperinsulinemic clamp where plasma insulin concentrations are supraphysiological. This should be taken into consideration when

interpreting our results because high insulin level may also contribute to a response to hypoglycemia. Third, we studied a sample of nondiabetic subjects with intact sympathoadrenal counterregulation mechanisms and we cannot exclude the possibility that electrocardiographic changes caused by hypoglycemia may be somewhat different in diabetic patients. Especially, we can speculate that in diabetic patients with blunted sympathoadrenal responses to hypoglycemia also, ECG changes may be attenuated. However, further investigation in this respect with diabetic patients is needed.

In summary, the results of the present study suggest that hyperinsulinemic hypoglycemia induces a cluster of ECG alterations that occur in atrioventricular conduction, ventricular depolarization, and ventricular repolarization. These changes may be of clinical importance with respect to adverse cardiovascular effects of hypoglycemia. Furthermore, we also found that counterregulatory epinephrine response is closely associated with morphological changes in T waves, suggesting a direct link between counterregulatory adrenergic activation and ventricular repolarization.

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