Insulin prolongs the QTc interval in humans

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Insulin prolongs the QTc interval in humans. Am J Physiol Regulatory Integrative Comp Physiol 279: R2022–R2025, 2000.—Insulin hyperpolarizes plasma membranes; we tested whether insulin affects ventricular repolarization. In 35 healthy volunteers, we measured the Q-T interval during electrocardiographic monitoring in the resting state and in response to hyperinsulinemia (euglycemic 1-mU·min⁻¹·kg⁻¹ insulin clamp). A computerized algorithm was used to identify T waves; Bazett’s formula was employed to correct Q-T (QTc) by heart rate (HR). In the resting state, QTc was inversely related to indexes of body size (e.g., body surface area, norepinephrine levels (161 ± 12 to 184 ± 10 pg/ml, P < 0.001) but not to indexes of body fatness. During the clamp, HR (67 ± 1 to 71 ± 1 beats/min, P < 0.0001) and plasma norepinephrine levels (161 ± 12 to 184 ± 10 pg/ml, P < 0.001) increased. QTc rose promptly and consistently, averaging 428 ± 6 ms between 30 and 100 min (P = 0.014 vs. the resting value of 420 ± 5 ms). Fasting serum potassium (3.76 ± 0.03 mM) declined to 3.44 ± 0.03 mM during insulin. After adjustment for body size, resting QTc was directly related to fasting plasma insulin (partial r = 0.43, P = 0.01); furthermore, QTc was inversely related to serum potassium levels both in the fasting state (partial r = −0.16, P < 0.04) and during insulin stimulation (partial r = −0.47, P = 0.003). Neither resting nor clamp-induced QTc was related to insulin sensitivity. Physiological hyperinsulinemia acutely prolongs ventricular repolarization independent of insulin sensitivity. Both insulin-induced hypokalemia and adrenergic activation contribute to this effect.

insulin action; heart rate; Q-T interval; ventricular repolarization; hypokalemia; sympathetic activation

THE Q-T INTERVAL on the electrocardiogram (ECG) measures the duration of repolarization of ventricular myocardium. A long Q-T signals an increased risk for arrhythmias (4) and sudden death (2), particularly in postinfarction patients (1) but also in apparently healthy people (20). The Q-T interval is characteristically prolonged in diabetes and has been related to unexplained cases of sudden overnight death in diabetic patients on insulin treatment (10). Q-T lengthening has been reported in other insulin-resistant states such as obesity (9). In a population-based survey, Q-T prolongation was associated with fasting plasma glucose and insulin concentrations as well as with glucose levels measured after oral glucose loading (7). On these grounds, it was postulated that hyperinsulinemia and/or glucose intolerance were causally related to a long Q-T. Direct proof of insulin or glucose effects on Q-T is, however, lacking.

Insulin exerts a prompt powerful action to increase transmembrane potential (25). After application of physiological amounts of insulin, the electrical potential across the plasma membrane of adipocytes, skeletal, and cardiac myocytes increases by a few millivolts due to the accumulation of negative charges on the inner side of the membrane (26). Because the Na⁺-K⁺ pump is electrogenic, stimulation of Na⁺-K⁺-ATPase could explain insulin-induced hyperpolarization. In excitable cells, such as cardiac myocytes, the predicted functional consequence of insulin-induced hyperpolarization is a lengthening of the repolarization phase. The present study was undertaken to directly test this hypothesis by measuring the Q-T interval in nondiabetic volunteers in the resting condition and during euglycemic hyperinsulinemia.

METHODS

Thirty-five normotensive volunteers were studied (Table 1). All had normal oral glucose tolerance, liver, renal, and endocrine function tests; none were taking any medications. The investigation was approved by the Institutional Review Board, and all subjects gave informed consent.

Body composition was evaluated by electrical biimpedance. Each subject received a euglycemic insulin clamp, which was carried out after an overnight (12–14 h) fast and consisted of 100 min of insulin infusion at a rate of 1 mU·min⁻¹·kg⁻¹ (6). A polyethylene catheter was inserted into an antecubital vein for the infusion of glucose and insulin. Another catheter was threaded into a wrist vein retrogradely, and the hand was placed in a heated box (60°C) for the sampling of arterialized blood. After instrumentation, the subjects rested at least 30 min in the supine position; the following 40 min constituted the basal period. Throughout the study, electrocardiographic recording was performed with the use of a bipolar lead frequency-modulation system (Remco-Cardioline, Milano, Italy) and both an inferior and a precordial lead.

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Table 1. Clinical characteristics and metabolic data

<table>
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<tr>
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<th>Mean</th>
<th>Range</th>
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<tr>
<td>n</td>
<td>35</td>
<td></td>
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<tr>
<td>Gender, M/F</td>
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<td>Age, years</td>
<td>36 ± 1</td>
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<tr>
<td>Weight, kg</td>
<td>84 ± 3</td>
<td>42–135</td>
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<td>BMI, kg·m⁻²</td>
<td>30.4 ± 1</td>
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<td>Fat mass, %</td>
<td>32 ± 2</td>
<td>14–44</td>
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<td>FFM, kg</td>
<td>54 ± 2</td>
<td>34–76</td>
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<td>WHR, cm·cm⁻¹</td>
<td>0.84 ± 0.02</td>
<td>0.59–1.04</td>
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<td>Fasting plasma glucose, mM</td>
<td>5.1 ± 0.1</td>
<td>4.2–6.0</td>
</tr>
<tr>
<td>Fasting plasma insulin, pmol/l</td>
<td>91 ± 5</td>
<td>53–195</td>
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<tr>
<td>Steady-state plasma glucose, mM</td>
<td>5.0 ± 0.1</td>
<td>4.2–6.0</td>
</tr>
<tr>
<td>Steady-state plasma insulin, pmol/l</td>
<td>652 ± 28</td>
<td>357–1,087</td>
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<td>M value, μmol·min⁻¹·kg FFM⁻¹</td>
<td>40 ± 2</td>
<td>15–61</td>
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Values are means ± SE. BMI, body mass index; M, male; F, female; FFM, fat-free mass; WHR, waist-to-hip ratio.

In six subjects, the study was repeated on a different day (in randomized order to the clamp) with the use of an identical protocol, except that the insulin infusion was replaced by a saline infusion. At the end of the 100-min infusion, subjects were asked to stand up and then resume the supine position over a period of 5 min.

**ECG processing.** The ECG was digitized at 250 samples/s with a 12-bit/sample precision and stored in a binary format. The selected 250-Hz frequency allows detection of R-R oscillations up to 4 ms. The ECG was processed with the use of extensively tested algorithms (23) to detect the QRS complex and the R-wave reference point by a derivative/amplitude criterion, without interpolation of the original signal. For the Q-T interval, a computerized algorithm was used to identify the onset of QRS and the end of the T wave on the precordial lead (with the use of a derivative filter applied to an observation interval on the ECG signal centered on the theoretical trend 0.4 × R-R1/2, on the basis of threshold-trespassing deflection with reference to the baseline signal) (23). Q-T varies inversely with the heart rate (HR); the duration of recovery decreases as the rate of activation increases. For this reason, Q-T is corrected with reference to the baseline signal (23). Q-Tc was directly related to the fasting plasma insulin concentrations (31 ± 4 μg/ml) did not change after insulin (37 ± 8 pg/ml), whereas plasma norepinephrine levels rose (from 161 ± 12 to 184 ± 10 pg/ml, P < 0.001). Fasting serum potassium concentrations (3.76 ± 0.03 mM) declined to 3.44 ± 0.03 mM (P < 0.0001) during the 40- to 100-min time period of insulin administration.

In bivariate regression adjusting for BSA, resting Q-Tc was directly related to fasting plasma insulin concentrations (Fig. 2); an inverse association with M values fell short of statistical significance. After adjustment for BSA, Q-Tc values were reciprocally related to serum potassium concentrations both in the basal condition and during insulin administration (Fig. 2).

![Fig. 1. Time course of heart rate (top), Q-T interval (middle), and Q-Tc (bottom) during resting conditions and during 100 min of euglycemic hyperinsulinemia in 35 nondiabetic subjects. ■ Means ± SE. bpm, Beats/min.](http://ajpregu.physiology.org/ by 10.220.32.247 on July 5, 2017)
In the time-control experiments, there was no significant change in either HR or QTc (data not shown). Standing up resulted in tachycardia (to a peak of 77 ± 2 beats/min, P < 0.0001), which was accompanied by a rise in QTc (to 454 ± 6 ms, P < 0.0001).

DISCUSSION

The present study demonstrated that acute physiological hyperinsulinemia prolongs the QTc interval. This effect 1) was prompt, being already fully established after 30 min of insulin infusion (Fig. 1); 2) did not differ in men vs. women, nor was it dependent on obesity; and 3) was unrelated to insulin-mediated glucose uptake. The finding explains previous observations that QTc lengthens after a meal in concomitance with a rise in HR (15). In addition, the fact that it is the hyperinsulinemia, rather than insulin resistance, that is responsible for QTc prolongation makes it possible to extrapolate this acute effect of insulin to a chronic condition. In fact, in insulin-resistant individuals, compensatory hyperinsulinemia may act unopposed on membrane polarization, thereby leading to persistent QTc lengthening. In keeping with this prediction, QTc has been found to be prolonged in states of insulin resistance, such as diabetes and obesity, even in the absence of autonomic neuropathy (9, 10). Our finding (Fig. 2) that the resting QTc was positively related to the degree of fasting hyperinsulinemia lends further support to this interpretation.

With regard to the mechanism of insulin-induced hyperpolarization, the finding that QTc and serum potassium levels were reciprocally related suggests that stimulation of cellular potassium uptake is the common mechanism for both insulin-induced hyperpolarization and insulin-induced hypokalemia. In studies employing the perfused forearm technique, we have shown that insulin stimulates potassium uptake by forearm tissues in a manner that is ouabain inhabitable and independent of concomitant forearm glucose uptake (8). Pertinent in this regard is the evidence from in vitro studies in mollusks that extracellular application of insulin directly hyperpolarizes neurons of the abdominal ganglion (22). Thus in both excitable and nonexcitable cells, insulin acts directly on the cell membrane to shift extracellular potassium into the cytoplasm, thereby hyperpolarizing the membrane (8, 22, 25, 26). In excitable tissues, hyperpolarization prolongs the repolarization phase either by increasing the temporal dispersion of action potential recovery or through early afterdepolarizations (12).

Q-T lengthening can also result from adrenergic activation; as in the case of insulin, this effect is mediated by hypokalemia (13). In healthy volunteers, epinephrine administered intravenously to levels similar to those seen after myocardial infarction causes an increase in systolic blood pressure and HR, a decrease in diastolic blood pressure and T-wave amplitude, and an increase in QTc (18). All of these responses can be prevented by pretreatment with α- or β-blockade (18).

During insulin infusion, plasma norepinephrine levels increased significantly despite maintenance of euglycemia, indicating sympathetic stimulation. This phenomenon results from a stimulatory action of insulin on midbrain nuclei that dispatch excitatory impulses to sympathetic neurons and inhibitory influences to the vagus (21). Thus physiological hyperinsulinemia reinforces its effect on membrane potential and serum potassium concentrations via sympathetic activation.

In conclusion, physiological hyperinsulinemia causes QTc prolongation both directly and through sympato-

![Diagram](http://ajpregu.physiology.org/)

Fig. 3. The physiological system connecting plasma insulin concentrations with serum potassium levels and the activity of the autonomic nervous system (ANS). (+) And (-) indicate stimulation and inhibition, respectively. See text for explanation.
thetic activation, the common mechanism (and mani-
manifestation) being the transfer of potassium ions from the 
extracellular to the intracellular space.

Perspectives

The present results can be integrated with existing 
information to delineate a complex feedback system (Fig. 
3) regulating a number a vital functions. In this system, 
plasma insulin and adrenergic activity are hormonal ef-
factors, serum potassium concentrations constitute a 
common interacting relay, and membrane potential is the 
output. Thus both plasma insulin and cate-
cholamines lower serum potassium by promoting its 
uptake into cells (5, 8). On the other hand, insulin en-
highens adrenergic activity, whereas adrenergic stimula-
tion (mostly through α2-receptors), in turn, inhibits in-
ulin release (16). The physiological operation of this 
system is best illustrated by the response to feeding. The 
rise in circulating insulin activates the sympathetic 
branch of the autonomic nervous system, thereby prepar-
ing the hemodynamic (e.g., splanchic vasodilatation) and 
thermogenic adaptation to feeding. Together with 
catecholamines, insulin stores alimentary potassium by 
transferring it into cells as well as sparing it from urinary 
loss. This ionic shift and other direct membrane effects of 
insulin (26) hyperpolarize cell membranes, thereby 
strengthening their refractoriness to electrical stimuli. 
One consequence of this membrane change in the cardio-
vascular system is a prompt reduction in HR variabil-
ity (14). Another one is attenuation of adrenergic-mediated 
vascular smooth muscle cell contraction (19). The serum 
level of potassium is set to serve as a modulator of the 
combined action of insulin and catecholamines. Thus 
hyperkalemia depresses the insulin-secretory response to 
glucose (17), whereas hyperkalemia downregulates sym-
pathetic activity (13).

A key element of this physiological system is that it is 
not tied with insulin’s actions on glucose metabolism. In 
fact, the effects of insulin on serum potassium (8), HR 
variability (14), and membrane polarization (as shown in 
the present work) are all independent of insulin-mediated 
glucose utilization. Therefore, in insulin-resistant states in 
which chronic hyperinsulinaemia ensues as a 
compensatory response, the membrane effects of insulin 
are not attenuated by insulin resistance. Consequently, 
the risk of cardiac arrhythmias is enhanced; this may 
constitute one basis for the increased cardiovascular risk of 
insulin-resistant states (11).

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