

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 1999, 100:e149

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX
72514

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ISSN: 1524-4539

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QTc Dispersion, Hyperglycemia, and Hyperinsulinemia

To the Editor:

QTc dispersion is an important predictor of cardiac mortality. In the Rotterdam Study,¹ persons in the highest tertile (>60 ms) relative to the lowest tertile (<39 ms) of QTc dispersion had a 2-fold risk of cardiac death. The Rotterdam Study also confirms that QTc dispersion is larger in diabetic than in nondiabetic persons. QTc duration and QTc dispersion are associated with plasma glucose and insulin levels,² but their relative contributions to each are still unclear. We evaluated the effect of acute hyperglycemia, with or without the accompanying hyperinsulinemia, on QTc duration and QTc dispersion in normal subjects.

We studied 27 healthy volunteers (17 men and 15 women) aged 49 ± 6 years (mean \pm SD). All subjects were given a hyperglycemic glucose clamp in which plasma glucose concentrations were acutely raised with a bolus injection of 0.33 g/kg glucose (50% solution) followed by a 30% glucose infusion to achieve steady-state plasma glucose levels of ≈ 15 mmol/L for 120 minutes. On another occasion, which was separated from the first by at least a 3-day interval and in random order, the subjects underwent the same hyperglycemic clamp plus octreotide administration (25 μ g as IV bolus followed by a 0.5 μ g/min infusion) to block the release of endogenous insulin. All tests were made with the aid of an artificial pancreas (Biostator). Electrocardiograms were recorded with a standard resting 12-lead ECG at 50 mm/s. QT interval analysis was done by a cardiologist who was blinded regarding other information. QT intervals were corrected with Bazett's formula ($QTc = QT/R\text{-}R$); QTc dispersion was calculated as the interlead variability of QTc interval ($QTc \text{ dispersion} = QTc_{\text{max}} - QTc_{\text{min}}$).

During clamp administration, plasma glucose stabilized at 15 mmol/L, and plasma insulin showed a biphasic pattern of response, with an early rise at 10 minutes (327 ± 89 pmol/L) followed by a gradual and sustained increase (456 ± 120 pmol/L). QTc increased from 413 ± 26 to 442 ± 29 ms ($P < 0.05$) at the end of the clamp administration, and QTc dispersion increased from 32 ± 9 to 55 ± 12 ms ($P < 0.01$). Basal and clamped plasma glucose levels in the octreotide study were not significantly different from those of the control study; glucose-stimulated insulin responses were markedly reduced by octreotide (105 ± 36 pmol/L at 10 minutes and 57 ± 16 pmol/L at 120 minutes). QTc and QTc dispersion increases in the octreotide study did not differ from those recorded in the control study.

Acute hyperglycemia in normal subjects produces significant increases of QTc and QTc dispersion that persist during oct-

reotide infusion, which suggests a minor role for insulin. Hyperglycemia may induce QT changes by increasing the cytosolic calcium content,³ by stimulating sympathetic activity,⁴ or both. These results may offer a novel mechanism through which hyperglycemia may add to the elevated cardiovascular risk of the diabetic patient.

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Response

Our report from the Rotterdam Study mainly concerns the prognostic association of QTc dispersion with future cardiac morbidity and mortality. Our study was not suitable for elucidating the mechanism underlying this association. Drs Marfella, Rossi, and Gugliano report a study that attempts to clarify part of the mechanism leading to prolonged QTc and increased QTc dispersion. However, caution should be taken interpreting the data because other factors, such as the intrinsic effects of octreotide or the change of electrolyte levels associated with massive glucose uptake, may also affect ventricular repolarization. We thank Drs Marfella, Rossi, and Guigliano for providing these interesting results, and we look forward to future results.

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