Elevated plasma fatty acid concentrations prolong cardiac repolarization in healthy subjects\textsuperscript{1,2}

Raffaele Marfella, Lorenita De Angelis, Francesco Nappo, Daniela Manzella, Mario Siniscalchi, Giuseppe Paolisso, and Dario Giugliano

ABSTRACT

Background: High fatty acid concentrations have been shown to stimulate sympathetic nervous system activity, which may modify ventricular repolarization and thus the Q-T interval on electrocardiogram recordings.

Objective: The aim of this study was to investigate whether acute elevations of plasma fatty acid concentrations influence the corrected Q-T interval (Q-Tc), Q-Tc dispersion, and sympathetic nervous system activity in healthy nonobese subjects.

Design: Thirty-two healthy subjects (\(\bar{x}\) ± SD: 48 ± 7 y of age) received an infusion of 10% triacylglycerol emulsion plus heparin (a bolus of 200 U followed by 0.2 U min\(^{-1}\) · kg body wt\(^{-1}\) for 180 min); on another occasion and in random order, the same subjects received a saline infusion.

Results: Compared with the saline infusion, infusion of 10% triacylglycerol emulsion increased plasma fatty acids (\(P < 0.001\)) and was associated with an increase in mean blood pressure (\(P < 0.05\)), heart rate (\(P < 0.05\)), Q-Tc (\(P < 0.01\)), Q-Tc dispersion (\(P < 0.01\)), and plasma epinephrine (\(P < 0.005\)). Furthermore, individual changes in plasma epinephrine correlated with changes in Q-Tc (\(r = 0.60, P < 0.001\)) and Q-Tc dispersion (\(r = 0.53, P < 0.02\)) even after adjustment for age, sex, and body mass index (\(P < 0.03\) for all correlations). Only changes in plasma fatty acids (\(P = 0.04\)) and plasma epinephrine (\(P = 0.006\)) concentrations were significantly and independently associated with the lengthening of the Q-T interval.

Conclusion: Our study showed that elevated plasma fatty acid concentrations might affect cardiac repolarization, at least in part because of an increase in plasma catecholamines.


KEY WORDS Fatty acids, Q-T interval, Q-Tc dispersion, catecholamines, cardiac repolarization

INTRODUCTION

Elevated plasma fatty acid concentrations have been associated with an increased number of ventricular premature complexes and sudden death in nondiabetic subjects (1) and in nonischemic diabetic patients (2). High fatty acid concentrations have been shown to stimulate sympathetic nervous system (SNS) activity in rats (3) and to activate calcium channels in ventricular myocytes (4). Both fatty acid–related SNS overactivity and detergent effects of fatty acid on plasma membrane composition (5) might explain the occurrence of arrhythmia and sudden death in obese subjects (6), in whom elevated fatty acid concentrations is a common finding (7).

It is widely accepted that the SNS may influence ventricular electrical activity by modifying ventricular repolarization and thus the Q-T interval on electrocardiogram recordings (8). A prolonged heart rate–adjusted Q-T interval (corrected Q-T interval; Q-Tc) is a risk factor for sudden death in patients with the long-Q-T interval syndrome and in myocardial infarction patients (9). Interestingly, obesity (10) is associated with a rise in plasma fatty acid concentrations and a lengthening of the Q-T interval, whereas the opposite occurs in patients after weight loss (11). Because changes in plasma fatty acid concentrations may exert a stimulatory effect on sympathetic activity (6), one cannot exclude that a rise in fatty acid plasma concentrations might be responsible for the prolongation of the Q-T interval. The aim of this study was to investigate the effect of acute elevations in plasma fatty acids on the Q-Tc, Q-Tc dispersion, and sympathetic activity in healthy, nonobese subjects.

SUBJECTS AND METHODS

Experimental design

Thirty-two healthy subjects volunteered for the study after a clear explanation of its experimental nature. All subjects had normal blood pressure, had no diabetes or hyperlipidemia, had no family history of premature vascular disease, and were non-smokers. All subjects were following a weight-maintaining diet providing 250 g carbohydrate/d and had no recent change in body weight or intercurrent illness (Table 1). All subjects gave informed consent to participate in the study, which was approved by the ethical committee of our institution.

After an overnight fast, all subjects received an infusion of 10% triacylglycerol emulsion (Intralipid; Pharmacia, Uppsala, Sweden). The infusion contained 25% of the daily energy requirement of each subject and was provided at a constant rate of 1.5 mL/min, which was sufficient to maintain constant plasma fatty acid concentrations throughout the entire study period.

REFERENCES

1. From the Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples.
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TABLE 1
Characteristics of the study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48 ± 7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.81 ± 0.04</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2 ± 1.7</td>
</tr>
<tr>
<td>Fasting plasma fatty acids (mmol/L)</td>
<td>405 ± 87</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>2-h Plasma glucose (mmol/L)</td>
<td>6.3 ± 0.8</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td>62.3 ± 12</td>
</tr>
<tr>
<td>Fasting plasma LDL cholesterol (mmol/L)</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>Fasting plasma HDL cholesterol (mmol/L)</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Fasting plasma triglycerol (mmol/L)</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>85.1 ± 2.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77.2 ± 7.8</td>
</tr>
<tr>
<td>Q-Tc (ms)</td>
<td>361 ± 19</td>
</tr>
<tr>
<td>Q-Tc dispersion (ms)</td>
<td>31.3 ± 8</td>
</tr>
<tr>
<td>Plasma epinephrine (pmol/L)</td>
<td>219 ± 25</td>
</tr>
<tr>
<td>Plasma norepinephrine (pmol/L)</td>
<td>1.9 ± 0.6</td>
</tr>
</tbody>
</table>

* x ± SD; n = 32 (15 men and 17 women). Q-Tc, corrected Q-T interval.

Sweden) plus heparin (a bolus of 200 U followed by 0.2 U·min⁻¹·kg body wt⁻¹) for 180 min. On another occasion, and in random order, the same subjects received a control infusion of saline solution (0.9% NaCl) that was matched to the overall volume and duration of the 10% triacylglycerol emulsion infusion. No more than 1 wk elapsed between the 2 studies in the same subject. A subset of 6 subjects also received an infusion of propranolol (100 μg/kg over 10 min followed by 1 mg·kg⁻¹·min⁻¹; Inderal, Zeneca, Milan, Italy), followed 10 min later by an infusion of 10% triacylglycerol emulsion plus heparin. Heart activity was recorded with a standard resting 12-lead electrocardiogram at 50 mm/s in the basal state and at the end of the infusions. A cardiologist who was blinded to other information conducted the Q-T interval analysis. Q-T intervals were corrected with Bazett’s formula (Q-Tc = Q-T/√R-R) (12); Q-Tc dispersion was calculated as the standard deviation of the Q-Tc values. Blood pressure and heart rate at baseline and during and at the end of the infusion were monitored in real time by using a Finapres apparatus (Ohmeda, Englewood, CO) (13).

Analytic methods

Plasma glucose was determined with the glucose oxidase method (Autoanalyzer; Beckman, Fullerton, CA). Blood samples for insulin determination were collected into heparin-containing tubes. After centrifugation (2500 × g, 5 min, 15°C), serum insulin was determined by using a commercially available radioimmunoassay kit (Sorin Biomedical, Milan, Italy; CV: 3.2 ± 0.3%). Plasma fatty acids were determined according to the method of Dole and Meinertz (14). Plasma epinephrine and norepinephrine were determined by HPLC.

RESULTS

Mean blood pressure was calculated as diastolic blood pressure plus one-third of pulse pressure. Individual changes in plasma hormone concentrations were calculated as the difference between the values found at 180 min and baseline values. To approximate normal distribution, insulin concentrations were log-transformed and then back-transformed for final presentation in standard units. Changes over time between treatments were assessed by analysis of covariance with the time 0 values as the covariate. Pearson’s product-moment correlation coefficients were used. Partial correlation allowed us to test the relation between 2 variables independent of a covariate. Multivariate analysis allowed an evaluation of the independent role of age, body mass index (BMI), and change in fatty acid concentrations on the lengthening of the Q-T interval. A P value of 0.05 was chosen as the level of significance. SPSS (version 10.0; SPSS Inc, Chicago) was used for the analyses.

TABLE 2
Changes in plasma metabolic indexes occurring during the control and 10% triacylglycerol emulsion infusions

<table>
<thead>
<tr>
<th>Metabolic Index</th>
<th>Control saline infusion</th>
<th>Triacylglycerol emulsion</th>
<th>P (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids (mmol/L)</td>
<td>405 ± 87</td>
<td>449 ± 99</td>
<td>435 ± 90</td>
</tr>
<tr>
<td>Plasma triglycerol (mmol/L)</td>
<td>1.6 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Plasma insulin (pmol/L)</td>
<td>61 ± 12</td>
<td>68 ± 16</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.2 ± 0.6</td>
<td>5.4 ± 0.5</td>
<td>5.3 ± 0.6</td>
</tr>
<tr>
<td>Plasma epinephrine (pmol/L)</td>
<td>219 ± 24</td>
<td>222 ± 21</td>
<td>209 ± 24</td>
</tr>
<tr>
<td>Plasma norepinephrine (pmol/L)</td>
<td>1.9 ± 0.6</td>
<td>2.1 ± 0.5</td>
<td>2.0 ± 0.6</td>
</tr>
</tbody>
</table>

* x ± SD; n = 32.

²Significantly different from 0 min (baseline); ²P < 0.01, ⁴P < 0.05.
Individual changes in plasma fatty acid concentrations correlated with changes in the Q-Tc ($r = 0.63$, $P < 0.001$), Q-Tc dispersion ($r = 0.54$, $P < 0.02$), and plasma epinephrine concentrations ($r = 0.69$, $P < 0.005$). Furthermore, individual changes in plasma epinephrine also correlated with changes in the Q-Tc ($r = 0.60$, $P < 0.01$) and Q-Tc dispersion ($r = 0.53$, $P < 0.02$). All such changes were still significant after adjustment for age, sex, and BMI ($P < 0.03$ for all correlations). In the stepwise multivariate analysis, the independent role of age, BMI, waist-to-hip ratio, and change in plasma fatty acid concentrations on lengthening of the Q-T interval was investigated. The whole model explained 47% of the variability in the lengthening of the Q-T interval with BMI ($P < 0.05$), and changes in plasma fatty acid concentrations ($P < 0.001$) were significantly and independently associated with the dependent variable. Addition of changes in plasma epinephrine concentrations among the independent variables increased the significance of the model, allowing it to explain 63% of the variability of the lengthening of the Q-T interval. Nevertheless, in such a model, only changes in plasma fatty acid ($P = 0.04$) and plasma epinephrine ($P = 0.006$) concentrations were significantly and independently associated with the lengthening of the Q-T interval.

**DISCUSSION**

Our study showed that acute increases in plasma fatty acid concentrations produce a lengthening of both the Q-Tc and Q-Tc dispersion in healthy subjects. The length of the Q-T interval, which is easily obtained from the use of a standard resting electrocardiogram, represents the time interval between the start of activation of the ventricle and the completion of its repolarization. The Q-T interval is influenced by the autonomic tone and represents an index of myocardial refractoriness and electrical stability; this is a critical determinant of ventricular fibrillation and sudden death (15). An association between a prolonged Q-T interval and sudden cardiac death was found in patients with coronary artery disease, congestive heart failure, and obesity (16, 17). Dispersion of repolarization is a consequence of the predominance of SNS activity and might be responsible for a high risk of ventricular fibrillation (18). Sympathetic stimulation unopposed by vagal activity might induce ventricular electrical instability, resulting in risk of arrhythmia and sudden death (19).

Fatty acid concentrations might affect Q-Tc and Q-Tc dispersion through a stimulation of SNS activity. In our study, acute elevations in fatty acid concentrations were associated with a rise in sympathetic activity, as evidenced by increased plasma catecholamine concentrations. The increased heart rate and the partial inhibition of the Q-Tc during the propranolol infusion also suggests an effect of fatty acid concentrations on cardiac repolarization mediated, at least in part, by an increase in plasma catecholamines. The link between plasma fatty acid concentrations and cardiac repolarization is also strengthened by the correlation between individual changes in plasma epinephrine concentrations and the Q-T or Q-Tc dispersion, a relation that is associated with changes in plasma fatty acid concentrations. Furthermore, in the multivariate analysis, changes in plasma fatty acids were independently associated with the lengthening of the Q-T interval. Whether the effect of fatty acid concentrations on the Q-Tc is mediated by the increase in plasma catecholamines or is also due to an effect on the central nervous system is unknown. Notwithstanding, the multivariate analysis encompassing age, BMI, waist-to-hip ratio, and both changes in plasma fatty acid and epinephrine concentrations showed that both plasma fatty acid and epinephrine concentrations remained statistically significant. Thus, plasma fatty acid concentrations, at least in part, are responsible for a direct effect on the lengthening of the Q-T interval. The latter possibility is also strengthened by evidence that prolongation of the Q-T interval might also result from a disturbed myocardial membrane function that, in turn, might be responsible for electrical instability (20). Indeed, it was shown previously that elevated fatty acid concentrations may inhibit Na⁺/K⁺-exchanging ATPase (21), resulting in disturbed myocardial membrane function. Nevertheless, only future studies specifically designed to assess such a possibility will clarify such a possible pathophysiological relation.

A significant correlation between postprandial lipemia and common carotid intima media thickness was found previously in healthy middle-aged men (22). Similarly, there is a relation between cardiovascular mortality and postprandial hyperlipemia (23). Because the elevations in triacylglycerol concentrations

![Image](https://academic.oup.com/ajcn/article-abstract/73/1/27/4729640/31/27272940 by guest on 09 October 2018)
obtained in our artificial model were similar to those observed during the postprandial phase, it is possible that modifications in the Q-T interval may occur during this phase. To our knowledge, this topic has never been addressed.

In conclusion, our study showed that elevated plasma fatty acid concentrations might affect cardiac repolarization. Such an effect seems partially mediated by an increase in plasma catecholamine concentrations. Our results may offer a novel mechanism for explaining the relation between increased visceral fat and elevated cardiovascular risk.

REFERENCES