Major rapid weight loss induces changes in cardiac repolarization ☆

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Abstract

Introduction: Obesity is associated with increased all-cause mortality, but weight loss may not decrease cardiovascular events. In fact, very low calorie diets have been linked to arrhythmias and sudden death. The QT interval is the standard marker for cardiac repolarization, but T-wave morphology analysis has been suggested as a more sensitive method to identify changes in cardiac repolarization. We examined the effect of a major and rapid weight loss on T-wave morphology.

Methods and Results: Twenty-six individuals had electrocardiograms (ECG) taken before and after eight weeks of weight loss intervention along with plasma measurements of fasting glucose, HbA1c, and potassium. For assessment of cardiac repolarization changes, T-wave Morphology Combination Score (MCS) and ECG intervals: RR, PR, QT, QTcF (Fridericia-corrected QT-interval), and QRS duration were derived.

The participants lost on average 13.4% of their bodyweight. MCS, QRS, and RR intervals increased at week 8 ($p < 0.01$), while QTcF and PR intervals were unaffected. Fasting plasma glucose ($p < 0.001$) and HbA1c both decreased at week 8 ($p < 10^{-5}$), while plasma potassium was unchanged. MCS but not QTcF was negatively correlated with HbA1c ($p < 0.001$) and fasting plasma glucose ($p < 0.01$).

Conclusion: Rapid weight loss induces changes in cardiac repolarization. Monitoring of MCS during calorie restriction makes it possible to detect repolarization changes with higher discriminative power than the QT-interval during major rapid weight loss interventions. MCS was correlated with decreased HbA1c. Thus, sustained low blood glucose levels may contribute to repolarization changes.

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Introduction

Overweight and obesity are associated with increased all-cause mortality [1]. Thus, achieving a healthy body weight is a primary strategy for the prevention and management of obesity-related comorbidities [2]. However, weight loss due to intensive lifestyle change is not associated with a decrease in the number of cardiovascular events, at least not in individuals with established or incipient cardiovascular disease [3]. Furthermore, rapid weight loss has been shown to induce adverse changes in cardiac repolarization during very low calorie diets [4], and has in some cases been linked to arrhythmias and sudden death in healthy obese individuals [4–6].

It is well known that a prolonged cardiac QT interval is associated with an increased risk of torsades de pointes ventricular tachycardia (TdP) which may degenerate into lethal arrhythmias. Therefore, the QT interval is an important parameter when assessing arrhythmic risk [7]. As a consequence, monitoring the ECG during weight loss with low calorie diets in eating disorders has been recommended, even in the absence of electrolyte disturbances [5,8]. However, it is known from studies of the long QT syndrome (LQT) and drug-induced LQT that some patients will develop torsades de pointes despite having a normal QT interval [9].

Changes in T-wave morphology have been suggested to be more sensitive markers of repolarization disturbances than the QT interval [10] and T-wave morphology algorithms have recently received FDA 510(k) approval [11]. Furthermore, independent studies from FDA have recently associated T-wave morphology changes with drugs known for their arrhythmic risk [12]. The T-wave Morphology Combination Score (MCS) is a quantitative marker, which increases during blockade of the delayed rectifier HERG potassium channel (Kv11.1) [13]. Thus, increases in MCS may be associated with increased blockage of HERG channels [13,14], which may imply an increased risk of arrhythmias. Furthermore, both hypo- and hyperglycemia have been associated with HERG blockade [15], indicating that glycemic perturbations may interact with cardiac repolarization. In addition, LQT patients with loss of function mutations in the voltage-gated potassium channel KCNQ1 experience both hypoglycemia and repolarization disturbances [16], further indicating a link between metabolism and cardiac repolarization. Also, hypoglycemia is associated with increased mortality rates and sudden death [17].

Therefore, the purpose of this study was to assess the effect of a major and rapid weight loss [18] on the QT interval and T-wave morphology. The association between ECG parameters and glucose metabolism was also investigated.

Methods

Study design

The participants followed a low calorie diet (810 kilocalories per day, Cambridge Weight Plan Products ®) for 8 weeks. The dietary energy distribution was 46% from carbohydrate, 41% from protein, and 13% from fat. Daily intake of protein was at least 43.2 g, and intake of the essential fatty acids, linoleic and linolenic acid, was 3 g and 0.4 g, respectively. Dietary fiber intake was 7.2 g per day at minimum and the diet met all recommendations for daily intake of vitamins and minerals.

Fasting blood samples were collected at the beginning and at the end of the weight loss period (week 0 and week 8), and body weight was measured every week during the 8 weeks [18]. ECGs were acquired at week 0 and 8.

Study population

Inclusion criteria for the main study were a body mass index (BMI) between 30 and 40 kg/m^2, age between 18 and 65 years and otherwise normal health. Exclusion criteria were diabetes or other known illnesses that could affect glucose or lipid metabolism, pregnancy, and breastfeeding. Twenty-six participants entered the study and had ECG measurements performed at week 0 and week 8.

ECG acquisition

Standard ten-second 12-lead median ECGs were obtained using digital ECG recorders (GE Healthcare, Milwaukee, WI) at a sampling rate of 500 Hz, with the subject resting in the supine position. At least three consecutive ECGs were acquired from each participant at each acquisition session to ensure reproducible ECGs. For the consecutive ECGs acquired, the median values of the measurements were used. All ECGs were uploaded to the MUSE Cardiology Information System and the following ECG measurements were delineated using the 12SL algorithm that superimposes all 12 leads to find fiducial markers (12SL, GE Healthcare, Milwaukee, WI): mean RR, QT interval, Bazett corrected QT interval (QTcB), Fridericia corrected QT interval (QTcF), QRS duration and PR interval. Fiducial markers were manually reviewed.

Morphology Combination Score

MCS and its subcomponents (flatness, asymmetry and notches) were measured with QTGuard + (GE Healthcare, Milwaukee, WI). MCS was calculated from the first principal component (PC1) of the T-wave (defined from the j-point to the end of the T-wave). PC1 is the linear combination of all leads that results in the largest variance. In practice, PC1 often closely resembles lead V$_5$. The advantage of principal components is that it combines information from several leads, which minimizes noise and artifacts.

MCS is a unit-less combination of asymmetry, flatness, and notch scores as specified by Graff et al. [14]

$$MCS = asymmetry + 1.6 \cdot flatness + notch$$

The normal T-wave has a MCS value around 0.7. Increasing MCS values indicate deviations from the normal T-wave and such changes have been associated with blockage or loss of function of the cardiac potassium channels [13,14] (see Fig. 1 for examples of T-waves with normal and increased MCS).

Fasting blood samples

Fasting plasma potassium and HbA1c were measured by indirect potentiometry and turbidimetric immunoassay, respectively (Cobas 6000, Roche Diagnostics, USA).

Plasma glucose was measured with the glucose oxidase technique (YSI model 2300 STAT Plus; Yellow Springs Instruments, Yellow Springs, OH, USA).

Body fat percentage

Fat percentage was assessed using dual-energy X-ray absorptiometry (DXA) scanning (DXA, Hologic discovery A, Bedford, MA, USA).