T-Wave Amplitude Is Related to Physical Fitness Status

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Background: Abnormalities in repolarization may reflect underlying myocardial pathology and play a prominent role in arrhythmogenesis. The T-wave amplitude has been associated with cardiovascular outcome in patients with acute myocardial infarction (MI). Additionally, T-wave amplitude is considered a predictor of arrhythmias, as well as being related to an individual's inflammatory status. The combined influence of different variables, such as inflammation, cardiovascular risk factors and physical fitness status, on the T-wave amplitude has not been evaluated to date. The aim of this study was to identify factors that affect the T-wave amplitude.

Methods: Data from 255 consecutive apparently healthy individuals included in the Tel Aviv Medical Center Inflammation Survey (TAMCIS) were reviewed. All patients had undergone a physical examination and an exercise stress test, and different inflammatory and metabolic biomarkers (fibrinogen, potassium, and high-sensitivity C-reactive protein) were measured.

Results: Multivariate stepwise analysis revealed that the body mass index and the resting heart rate were significantly associated with the T-wave amplitude ($\beta = -0.34$, $P < 0.001$; $\beta = -0.19$, $P = 0.03$, respectively) in males, while the recovery rate and the usage of statins significantly affected the T-wave amplitude in females ($\beta = 0.36$, $P = 0.002$; $\beta = 0.35$, $P = 0.002$, respectively). Inflammatory variables had no significant effect on the T-wave amplitude of either gender.

Conclusions: In conclusion, the T-wave amplitude is linked to an individual's physical fitness and not to his/her inflammatory status.

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The QT interval and the T wave comprise the morphological representation of the ventricular phase of repolarization on an electrocardiogram (ECG).¹ Abnormalities in this phase reflect underlying myocardial pathology and play a prominent role in arrhythmogenesis. They have been shown in several studies to be correlated with increased cardiovascular mortality.^{2–4} Similarly, inflammation has emerged in recent years as a major constituent in the pathogenesis of cardiovascular diseases, with C-reactive protein (CRP) acting both as a marker and a predictor of adverse cardiac events.^{5,6} Yue et al. demonstrated that abnormal repolarization, as manifested in a prolonged QT interval and a low T-wave amplitude, was associated with increased inflammation parameters, such as CRP,

in a small cohort of patients with coronary artery disease.⁷

In another study, a higher T-wave amplitude in patients presenting with an acute myocardial infarction (AMI) who subsequently underwent thrombolysis was associated with a lower 30 day mortality, and a lesser chance of developing congestive heart failure or cardiogenic shock.⁸ The influence of inflammation, cardiovascular risk factors and physical fitness status on the T-wave amplitude in patients without known cardiac disease has not been evaluated to date. The aim of this study was to examine a large sample of apparently healthy individuals and determine whether the aforementioned association between ECG parameters and inflammation was still valid in a

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general population of subjects and when factoring in additional clinical parameters.

METHODS

Population

This study reviewed the data on all consecutive individuals included in the Tel Aviv Medical Center Inflammation Survey (TAMCIS) during 1 month.^{9,10} TAMCIS is a registry of individuals attending the Tel Aviv Sourasky Medical Center for routine screening health examinations. Exclusion criteria were underlying active inflammatory disease (arthritis, inflammatory bowel disease, etc., defined as hsCRP above 10 mg/L), use of beta blockers (since we are measuring resting heart rate and recovery rate), infections or other inflammatory conditions, such as MI, scheduled for surgery before study enrollment, and known cancer. The final sample consisted of 255 study participants who provided written informed consent according to the instructions of the Institutional Ethics Committee.

Definition of Atherothrombotic Risk Factors

Diabetes mellitus was defined as blood glucose of ≥ 126 mg/dL fasting or the use of insulin or oral hypoglycemic medications. Hypertension was defined as blood pressure readings of $\geq 140/90$ mmHg on two separate measurements or the use of antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol concentration or non-high-density lipoprotein (HDL) cholesterol concentrations above the recommended number according to the risk profile defined by the updated ATP III recommendations,¹¹ triglyceride concentrations of ≥ 200 mg/dL, or the use of lipid-lowering medications. Smokers were defined as individuals who smoked at least five cigarettes per day, while past smokers were those who had quit smoking for at least 30 days before the examination for study entry.

Laboratory Methods

High-sensitivity CRP (hs-CRP) concentration levels were calculated by the Behring BN II Nephelometer (DADE Behring, Marburg, Germany).¹² The white blood cell count (WBCC) was determined by the standard Coulter STKS electronic analyzer. Quantitative fibrinogen was measured by

the method of Clauss¹³ and a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) autoanalyzer.

ECG Analysis

All ECG charts were evaluated by a physician who was unaware of the subjects' clinical findings. Each chart was graded manually. Guided by Surawicz and Parikh's 2002 study,¹⁴ we chose to focus on the basic T-wave variable of amplitude and measured the T-wave amplitude in the lead with the tallest T wave. The metabolic equivalent rates (METs) were estimated according to the standard Bruce protocol previously described elsewhere.¹⁵ The Duke Treadmill score (TM score) was calculated using the following formula: TM score = exercise time (Bruce protocol) – (5 × ST deviation in mm) – (4 × TM angina index). The angina index was assigned a value of 0 if angina was absent, 1 if typical angina occurred during exercise, and 2 if angina was the reason the patient stopped exercising. Exercise-induced ST deviation was defined as the largest net ST displacement in any lead.¹⁶

The peak heart rate was recorded during the stress test. The resting heart rate was recorded before the beginning of the stress test after resting for 15 minutes. The recovery rate was measured at 1, 2, and 5 minutes after the stress test was stopped. We calculated the decline in heart rate at each interval compared to the peak heart rate.

Statistical Analysis

All data were summarized and displayed as mean $\pm$ standard deviation (SD) for the continuous variables (age, body mass index [BMI], hs-CRP, etc.), and as number of patients plus the percentage in each group for categorical variables (medication, cardiovascular risk factors, etc.). The crosstabs and descriptive procedures were used to produce frequencies of categorical variables and means $\pm$ SD of continuous variables. We used the Spearman's correlation test to evaluate the correlation of the results of selected variables acquired during the stress test (BMI, Recovery heart rate at 1 minute, Recovery heart rate at 5 minutes, Duke score time total exercise, Peak heart rate, Resting heart rate, QTc before effort) and the subject's T-wave amplitude. To assess which of the variables contributes to the variability of amplitude of the T-wave, we used a multivariate stepwise linear regression model, with the T-wave amplitude as the

Table 1. Baseline Characteristics of the Study Population (N = 255)

	Males (N = 173) N (%)	Females (N = 87) N (%)	P Value
Current smokers	33(19)	23(26)	0.21
Past smokers	31(18)	13(15)	0.49
Diabetes mellitus	4(2)	2(2)	0.99
Hypertension	7(4)	2(2)	0.536
Dyslipidemia	7(8)	7(8)	0.945
Ischemic heart disease	0	0	1
Prior stroke	2(1)	2(2)	0.31
Prior myocardial infarction	0	0	1
Asthma/COPD	7(4)	2(2)	0.324

COPD = chronic obstructive pulmonary disease.

dependent variable, and age, anthropometric variables (waist circumference, BMI), stress test variables (Duke score, resting heart rate, peak heart rate, recovery rate and METs), cardiovascular risk factor (diabetes, hypertension, dyslipidemia, smoking), inflammatory biomarkers (fibrinogen, potassium, and hs-CRP levels), medications (statins) as the independent ones using the stepwise enter method. The level of significance used for all of the above analyses was two tailed ($P < 0.05$). The SPSS statistical package was used to perform all statistical evaluation (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the total of 255 patients enrolled in the study, 173 (68%) were males and 81 (32%) were females. The mean age of the cohort was 46.0 ± 10.8 years (range: 20–77). The baseline medical characteristics and medical treatment of the study population are summarized in Tables 1 and 2, respectively. Their baseline metabolic and inflammatory values are presented in Table 3.

To assess the relationship between T-wave amplitude and a patient's cardiovascular fitness profile, we conducted a spearman's correlation test. Table 4 demonstrates the high degree of correlation between the T-wave amplitude and various variables measured on a standard stress test.

Next, we conducted a multivariate stepwise linear regression to assess which of the selected variables affect the repolarization phase. T-wave amplitude was the dependent variable, and age, an-

Table 2. Medications Used by the Study Participants

	Males (N = 174) N (%)	Females (N = 81) N (%)	P value
ACE Inhibitors	3(2)	1(1)	0.77
Aspirin	7(4)	1(1)	0.235
Beta-blockers	0	0	1
Angiotensin II blockers	3(2)	1(1)	0.77
Calcium blockers	1(1)	7(8)	0.495
Statins	16(9)	8(10)	0.863

thropometric variables (waist circumference, BMI), stress test variables (Duke score, resting heart rate, peak heart rate, recovery rate and METs), cardiovascular risk factor (diabetes, hypertension, dyslipidemia, smoking), inflammatory biomarkers (fibrinogen, potassium, and hs-CRP levels), medications (statins) were the independent variables. Table 5 lists the variables that had a significant effect on the T-wave amplitude. Gender emerged as being the most significant variable ($\beta = -0.47$, $P < 0.001$): the mean T-wave amplitude was 2.7 mm in females and 4.6 mm in males ($P = 0.001$). Other variables which were significantly related to the T-wave amplitude were the BMI ($\beta = -0.22$, $P < 0.001$) and the resting heart rate ($\beta = -0.14$, $P = 0.02$). Notably, inflammatory variables were not correlated with the T-wave amplitude. Figure 1 demonstrates the relation between BMI tertiles and the T-wave amplitude. As can be seen, there is a negative relation between BMI and T-wave amplitude. Since gender was the most significant factor to influence T-wave amplitude, we conducted another multivariate regression analysis on males and females with the same variables mentioned above: the BMI and the resting heart rate turned out to significantly influence the T-wave amplitude among the males, while heart rate recovery at 2 minutes and the use of statins were related to higher T-wave amplitudes among females (Table 5).

DISCUSSION

The results of this study on apparently healthy individuals demonstrated a correlation between abnormal repolarization, as evidenced by low T-wave amplitude, and the level of physical fitness, as evaluated by the resting heart rate and the recovery rate. We used the T-wave amplitude because it is

Table 3. Baseline Metabolic and Inflammatory Values According to Gender

	Males (N = 174) Median Value (Interquartile range)	Females (N = 81) Median Value (Interquartile range)	P Value
HDL mg/dl	47.5 (41.4–53.8)	60 (51–71)	<0.001
LDL mg/dl	119.0 (99–142)	108 (94–137)	0.137
HbA1c%	5.4 (5.2–5.7)	5.6 (5.2–5.8)	0.223
WBC N/mm ³	6.8 (5.8–7.9)	7 (5.7–7.9)	0.787
Fibrinogen mg/dl	276 ()	321 ()	<0.001
Hs-CRP mg/dl	2.5 (0.7–3.4)	4.4 (0.6–5.1)	0.193

HDL = high-density lipoprotein; LDL = low-density lipoprotein; HbA1c = hemoglobin A1c; WBC = white blood cells; Hs-CRP = high-sensitivity C-reactive protein.

Table 4. Univariate Correlations between Stress Test Variables and T-Wave Amplitude

Variable	R Correlation Coefficient	P Value
BMI (kg/m ²)	−0.23	<0.0001
Recovery heart rate at 1 minute	0.14	0.025
Recovery heart rate at 5 minutes	0.17	0.006
Duke score	0.27	<0.0001
Time total exercise	0.29	<0.0001
Peak heart rate	0.25	<0.0001
Resting heart rate	−0.24	<0.0001
QTc before effort	−0.17	0.007

QTc = corrected QT interval; BMI = body mass index.

simpler to measure than the corrected QT interval (QTc). The T wave is a marker of repolarization that has been investigated intensively in relation to cardiovascular morbidity and mortality¹⁷ and increased post-MI risk.⁴ Its clinical significance was shown in the Zutphen study in which males with higher T-wave amplitudes had a lower risk of cardiovascular death or MI,¹⁸ and in a GUSTO-I sub study, which showed higher T-wave amplitudes to be associated with lower 30-day mortality and lower risk of developing congestive heart failure or cardiogenic shock in patients presenting with an AMI who subsequently underwent thrombolysis.⁸

Yue et al.⁷ demonstrated a relationship between T-wave amplitude and inflammation in patients with coronary heart disease. Those authors hypothesized that there is an inflammation-repolarization ion channel link or, alternatively, that the correlation might be due to an inflammation-induced change in the autonomic nervous system which, in turn, affects heart rate variability and thus causes repolarization abnormalities. We sought to investi-

Table 5. Variables Affecting T-Wave Amplitude Using Linear Regression

		Beta Coefficient	P Value
Entire Cohort	Female gender	−0.47	<0.001
	Body mass index	−0.22	<0.001
	Resting heart rate	−0.14	0.02
Males	Body mass index	−0.34	<0.001
	Resting heart rate	−0.19	0.03
Females	Decline in heart rate from peak heart rate after 2 minutes of recovery	0.36	0.002
	Statins	0.35	0.002

Data is presented for the entire cohort and according to gender. The recovery rate was measured at 1, 2, and 5 minutes after the stress test was stopped. We calculated the decline in heart rate at each interval compared to the peak heart rate.

gate whether this hypothesis was still valid when accounting for the clinical parameters of heart rate, age, gender, waist circumference, physical status and medication. Interestingly, our results showed that the association between inflammation and abnormal repolarization disappears when regression analysis is applied and all the relevant clinical parameters are accounted for. Specifically, our results demonstrated that the T-wave amplitude has a significant association with the BMI and the resting heart rate in male subjects. This association is not surprising given that obesity is a known cardiovascular risk factor in both males¹⁹ and females.²⁰ Conversely, the resting heart rate, which is known to reflect the autonomic nervous system and represent the level of physical fitness, was an independent predictor of cardiovascular and all-cause mortality in both males and females who did and did not have a diagnosed cardiovascular

disease.²¹ Furthermore, the recovery heart rate after exercise was significantly correlated with the T-wave amplitude in our female subjects. A pathologic heart rate recovery was shown in earlier studies to confer increased cardiovascular risk.^{22,23} These changes could also be attributed to sympathetic-parasympathetic changes that are also present in patients with obesity.²⁴⁻²⁷

In conclusion, we believe that the T-wave amplitude is related to the general physical status of a patient. As such, the T-wave amplitude could serve as a marker of physical fitness. Future prospective studies will be needed to elucidate the prognostic value of these ECG variables in the general population.

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