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Increased T-Wave Complexity Can Indicate Subclinical Myocardial Ischemia in Asymptomatic Adults

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Abstract

Background—Altered ventricular repolarization and cardiovascular mortality are closely correlated and recent novel findings show that a distorted T-wave loop morphology is also strongly correlated with subsequent onset of myocardial infarction among stable angina patients. Therefore, we hypothesized that an abnormal T-wave complexity ratio (CR) can indicate vulnerability to myocardial ischemia in asymptomatic, apparently-healthy adults.

Methods—Healthy firefighters were enrolled in the current investigation where they completed symptom-limited, graded exercise treadmill testing (ETT) and 24-hr Holter ECG recording. The CR was automatically calculated using principal component analysis of the high-resolution Holter ECG signal then averaged over 24 hrs (CR_{24hrs}). Endpoints were manually analyzed from the ETT; recordings revealing horizontal ST-segment depression (≥ 1 mm) in two or more leads for at least 1 min during the peak of exercise were considered indicators of myocardial ischemia.

Results—104 firefighters (age 44 ± 8 years, 96% men) completed both ETT and Holter recording. Firefighters with positive endpoints ($n=34$, 33%) had higher CR_{24hrs} compared to those with negative endpoints (0.14 ± 0.06 vs 0.09 ± 0.04 , $p < 0.01$), there were no demographic differences between the two groups. After controlling for age, smoking status, hypertension, and obesity; an abnormal CR_{24hrs} ($\geq 20\%$) significantly predicted exercise-induced myocardial ischemia (odds ratio 4.6, $p=0.01$).

Conclusions—Increased T wave CR_{24hrs} can predict myocardial ischemia in asymptomatic middle age adults; this suggests that the distorted T wave loop morphology can reflect an altered ventricular repolarization caused by prolonged subclinical myocardial ischemia possibly due to early coronary artery disease.

Keywords

Principal Component Analysis; T wave Complexity; Repolarization; Myocardial Ischemia; Firefighters

BACKGROUND

Altered ventricular repolarization plays an essential role in the mechanism of cardiovascular mortality¹. Rooted in the assumption that the T-wave is monophasic and without notches;

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novel T-wave loop morphology descriptors that simultaneously quantify QT duration, T-wave shape, and ST/T wave morphology, have been previously suggested to quantitatively measure such alterations in ventricular repolarization². Obtained from the electrocardiogram (ECG), these novel T-wave loop morphology descriptors have been repeatedly linked to subsequent cardiovascular mortality in different populations^{3–8}. Recent novel findings⁹ have shown that a distorted T-wave loop morphology is strongly correlated with subsequent onset of myocardial infarction among stable angina patients; suggesting that altered repolarization indicates increased vulnerability to myocardial ischemia. Therefore, we hypothesized that a distorted T-wave loop morphology, measured by complexity ratio (CR), can predict myocardial ischemia in asymptomatic, apparently-healthy adults.

METHODS

Healthy on-duty professional firefighters recruited in the parent study, Surveying and Assessing Firefighters Fitness and Electrocardiogram (SAFFE study)¹⁰, were enrolled in the current investigation. All firefighters completed a symptom-limited, graded exercise treadmill testing (ETT) using standard Bruce protocol and a 24-hr Holter 12-lead ECG recording that was analyzed using SuperECG software (Mortara Instrument, Milwaukee, WI). The CR was automatically calculated using principal component analysis (PCA) of the high-resolution Holter ECG signal then averaged over 24 hrs (CR_{24hrs}). A CR_{24hrs} of 20% or more was previously suggested to resemble abnormal repolarization in healthy adults² and therefore was used to define the cutoff value for abnormal CR_{24hrs} in the current investigation. A reviewer blinded to all clinical data manually analyzed the endpoints from the ETT using X-Scribe software (Mortara Instrument); recordings revealing horizontal ST-segment depression (≥ 1 mm) and/or T wave inversion in 2 or more adjacent leads for at least 1 min during the peak of exercise were considered indicators of myocardial ischemia¹¹.

Principal Component Analysis

Instead of analyzing the inhomogeneity of T wave morphology from different ECG leads, PCA technique was previously developed to grossly estimate the morphological complexity of the multiple forms required to describe the T-wave using decomposition matrices to estimate the eigenvalues, which makes PCA more consistent due to being less dependent on time domain or precise determination of T wave offset. With the first eigenvalue component accounting for most repolarization energy compared to all 8 eigenvalues components, a calculated ratio between these components, usually referred to complexity ratio (CR), can accurately estimate the heterogeneity of repolarization. In the current investigation, the ratio of the 2nd to 1st eigenvalues of the spatial T-wave vector generated from the digital, minute-by-minute averaged 12-lead ECG was used as a measure of the complexity or heterogeneity of repolarization. CR constitutes the difference between the long and short T wave vectors in a three dimensional loop domain. A large CR (fatter loop) reflects a more dispersed, heterogeneous repolarization compared to a small CR (thinner loop) that reflects a normal, homogenous repolarization. A CR obtained over 24hrs (CR_{24hrs}) allows measuring the diurnal variability of ventricular repolarization².

Statistical Analysis

Continuous values are reported as mean $\pm$ standard deviation, and categorical variables are reported as frequency (%). Chi-square and independent t-test were used to compare the difference between firefighters with positive and negative endpoints. Step-wise logistic regression was used to predict myocardial ischemia on ETT; selected demographics and clinical data were entered in the first step and CR_{24hrs} was entered in the second step. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS for Windows (Version 17).

RESULTS

Professional firefighters (n=104, age 44±8 years, 96% men, 81% white) completed both ETT and 24 hour Holter recording. Table 1 shows sample demographics and differences between firefighters with positive (n=34, 33%) and negative endpoints (n=70, 67%). Compared to those with negative endpoints, firefighters with positive endpoints (max ST depression on peak ETT = 2.2±0.6 mm, range 1.3–3.5) had more firefighting experience, had higher systolic blood pressure, achieved faster heart rate and greater exercise tolerance on the ETT, and had larger T wave loop CR_{24hrs} (0.14±0.06 vs 0.09±0.04, p<0.01), there were no differences in age, sex, race, body mass index (BMI), waist circumference, or smoking status between the two groups. The average T wave loop CR_{24hrs} in the whole sample was 10.7±4.9%; a cutoff point of 20% or more approximates 2 standard deviations above the mean. Approximately, 17 firefighters (16.3%) had abnormal T wave loop CR_{24hrs}. Of note, the distorted T wave loop was independent from transient ST/T wave ischemic events documented during Holter recording ($\chi^2=0.005$, NS).

Using stepwise logistic regression, after controlling for age (years), smoking status (yes/no), hypertension rate (BP≥140/90 mmHg), and obesity rate (BMI≥30 kg/m²), T wave loop CR_{24hrs} was significant in the final model, explaining 18.4% of the predicted myocardial ischemia on ETT (odds ratio 4.6, p=0.01, Table 2). An abnormal CR_{24hrs} (≥20%) has shown 65% positive and 74% negative predictive values; 91% specificity, and 32% sensitivity to predict myocardial ischemia in asymptomatic firefighters. Figure 1 shows subclinical myocardial ischemia during the peak ETT of a firefighter with an abnormal CR_{24hrs}.

DISCUSSION

Continuous 24-hour Holter ECG recording allows measuring the diurnal variability of ventricular repolarization, our findings showed that 16% of firefighters in the current investigation had increased T wave loop CR_{24hrs}, which indicates a dispersed, heterogeneous ventricular repolarization, a marker of increased risk for arrhythmogenic mortality. After controlling for demographic and clinical indices previously reported to predict coronary artery disease (CAD) in firefighters (specifically hypertension, obesity, and smoking), those with fatter T wave loop (CR_{24hrs} ≥20%) were at least four times more likely to have exercise-induced myocardial ischemia on the ETT. Our findings are similar to previous studies where balloon-induced myocardial ischemia in catheterization lab was associated with transient alterations in T wave loop morphology mirroring a simultaneous repolarization dispersion.

Firefighters are at increased risk for cardiovascular mortality; approximately 39% of on-duty deaths in this population are due to CAD²¹. Almost one third of firefighters in the current investigation had exercise-induced myocardial ischemia during their peak ETT, which was much higher than previously reported rates of positive ETT in similar populations (13%)²². Firefighters for this study were recruited from Western New York (WNY), therefore, the high rate of abnormal ETT can be partially related to the fact that the county has the highest rates of cardiovascular diseases in the nation²³. Moreover, we have previously defined a higher rate of metabolic syndrome in professional firefighters at WNY compared to general population²⁴, which constitutes a marker for CAD. Interestingly, there were no differences between firefighters with positive and negative ETT in regard to traditional risk factors (age, sex, obesity, smoking, or hypertension) or other clinical indices (average heart rate, QRS duration, QTc duration, or transient ST/T wave ischemic events). However, firefighters with positive ETT were on average 3 years more experienced and had 6.5 mmHg higher systolic blood pressure compared to those with negative ETT, suggesting possibly higher rates of

occupational hazards exposure (e.g. carbon monoxide inhalation) and associated cardiovascular morbidity (e.g. elevated blood pressure and myocardial ischemia).

Myocardial ischemia induces electrophysiological alterations in action potentials, causing repolarization dispersion between normal and ischemic fibers and between epicardium and endocardium, establishing the basis for re-entrant depolarization dispersion currents and subsequent life-threatening ventricular arrhythmias²⁰. Even though not ideal, such minor electrical dispersion currents can be measured with surface electrical ECG measures²⁵. Berger et al²⁶ have demonstrated that repolarization lability, measured through beat-to-beat QT variance in patients with ischemic and non-ischemic cardiomyopathy, reflects a prolongation of the action potential due to alteration in calcium and potassium influx currents, in which most alteration happens in mildly symptomatic individuals where sudden cardiac death is most prevalent. In light of these mechanisms, the prevalent subclinical myocardial ischemia in the current investigation (33%), along with the associated repolarization dispersion (16%), can possibly explain the prevalent cardiac mortality previously reported in firefighters. Finally, the absent correlation between the distorted T wave loop (abnormal CR_{24hrs}) and the transient ST/T wave ischemic events, documented during *continuous* Holter recording, suggests that each has a different pathological mechanism in relation to myocardial ischemia. The altered ventricular repolarization pattern (abnormal CR_{24hrs}) can reflect prolonged subclinical myocardial ischemia possibly due to early CAD. Further investigation is needed to understand this relationship.

Limitations

There are no ETT gold standard criteria to identify myocardial ischemia in asymptomatic adults¹¹; the *clinical* criteria used to diagnose CAD are more rigid than that used in the current investigation (horizontal ST depression of 2mm vs 1mm, respectively). However, in populations with high prevalence of the disease (e.g. firefighters), a positive diagnostic test is usually more likely to indicate the outcome; some studies report that using more rigid criteria in screening asymptomatic firefighters might lack adequate sensitivity to detect CAD²². Since we were concerned with detecting repolarization dispersion caused by subclinical myocardial ischemia, rather than significant CAD, less rigid criteria (ST segment depression of 1mm) were used to define exercise-induced myocardial ischemia. Additionally, the very wide 95% CI of odds ratio in the multivariate analysis reflects the small number of subjects with abnormal repolarization dispersion in the sample (n=17, 16%); which requires a larger sample size to validate the results.

CONCLUSIONS

Subclinical myocardial ischemia in asymptomatic adults is strongly correlated with altered ventricular repolarization. Such minor alterations in ventricular repolarization were successfully recorded with surface ECG, which enables this novel study to improve the clinical utility of non-invasive 12-lead ECG to detect early CAD through evaluating the PCA of ventricular repolarization rather than relying solely on transient ST segment changes that might lack adequate predictive values.

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Figure 1. 12-lead ECG Revealing Exercise-Induced Myocardial Ischemia

This recording was taken at the peak of an exercise-treadmill testing of a 52 year-old healthy male firefighter, non-obese, and non-smoker. The recording shows horizontal ST depression >1mm in V4–V6 that lasted for 3 minutes after stopping the test. The average 24hrs T wave loop complexity ratio obtained from the Holter was 20%.

Table 1

Sample Demographics and Clinical Indices

Variable	All Subjects	Myocardial Ischemia on ETT		P value
	(n=104)	Negative (n=70)	Positive (n=34)	
Age (yrs)	43.6±7.7	42.8±7.9	45.6±5.7	0.07
Sex (% men)	96	96	97	NS
Race (% white)	81	83	79	NS
Firefighting Experience (yrs)	15.5±7.0	14.6±7.2	17.5±6.3	0.05
BMI (kg/m ²)	29.5±4.1	29.7±4.3	29.2±4.1	NS
Obesity (BMI≥30, %)	41	46	29	0.11
Waist Circumference (cm)	101.3±11.8	101.9±12.7	100.9±11.2	NS
Systolic BP (mmHg)	129.3±14.9	126.8±14.0	133.3±17.1	0.04
Diastolic BP (mmHg)	81.8±10.6	81.6±10.5	81.9±11.5	NS
HTN (BP≥140/90, %)	36	31	44	NS
Smoking Rate (%)	12	13	9	NS
Average 24 heart rate (beats)	76.6±9.9	76.9±9.1	75.3±10.7	NS
QRS duration (msec)	98.5±11.1	98.9±9.8	97.3±13.7	NS
QTc duration (msec)	409.2±32.9	407.8±28.9	403.7±29.7	NS
ST ischemic events (%)	13	10	15	NS
Max HR on ETT (% target)	92.7±7.5	91.4±7.3	96.0±7.1	0.01
METs achieved on ETT	11.8±2.5	11.5±2.7	12.6±1.8	0.01
T wave Loop CR _{24hrs}	0.11±0.05	0.09±0.04	0.14±0.06	0.01
Abnormal CR _{24hrs} (%)	16	6	32	0.01

All values are mean ± SD; (%): incidence rate; BMI: Body Mass Index; BP: Blood Pressure; HTN: Hypertension; HR: Heart Rate; ETT: Exercise Treadmill Testing; METs: Metabolic Equivalent Tasks; CR_{24hrs}: Average Complexity Ratio over 24 hrs

Table 2

Adjusted Logistic Regression Analysis for Selected Clinical Parameters and T wave Loop Complexity Ratio in Relation to Exercise-Induced Myocardial Ischemia

Parameter	Exercise-Induced Myocardial Ischemia n=34			
	β	P value	OR (95% CI)	Total R ²
Age (years)	0.05	0.11	-	-
Smoking Status	- 0.59	NS	-	-
Hypertension (BP $\geq$ 140/90)	0.44	NS	-	-
Obesity (BMI $\geq$ 30)	- 0.63	NS	-	-
Abnormal CR _{24hrs} ($\geq$ 20%)	1.52	0.01	4.6 (1.4–14.9)	18.4

BP: Blood Pressure; BMI: Body Mass Index; CR_{24hrs}: Average Complexity Ratio over 24 hrs.