# Exercise-Induced Repolarization Changes in Patients With Stable Coronary Artery Disease

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**Exercise is a classic trigger of ventricular arrhythmias in the setting of coronary artery disease (CAD). The aim of this study was to examine the changes of novel indexes of repolarization in patients with stable CAD who underwent exercise stress testing. Sixty-seven consecutive patients (mean age 62 ± 9 years, 60 men) who underwent treadmill exercise stress testing according to the Bruce protocol and completed the test without evidence of ischemia were enrolled. Baseline clinical and demographic characteristics were recorded, and indexes of repolarization such as corrected QT (QTc) interval, T peak-to-end (Tpe) interval, and Tpe/QT ratio were assessed at baseline and at peak exercise. A similar group of control subjects without CAD (n = 68, mean age 60 ± 11 years, 52 men) were also studied. All participants successfully completed the test. In the patient group, the QTc interval significantly increased from baseline to peak exercise (median 385 ms [25th percentile 357 ms, 75th percentile 407 ms] vs 418 ms [381 ms, 447 ms], p <0.001). The Tpe interval and the Tpe/QT ratio were also significantly increased at peak exercise (42 ms [36 ms, 60 ms] vs 78 ms [60 ms, 84 ms], p <0.001; and 0.17 [0.14, 0.22] vs 0.21 [0.16, 0.25], p = 0.015). In the control group, the QTc interval did not change significantly, the Tpe interval decreased at peak exercise (62 ms [41 ms, 80 ms] vs 48 ms [40 ms, 78 ms], p = 0.05), and the Tpe/QT ratio did not show a significant change (0.18 [0.12, 0.22] vs 0.16 [1.14, 0.21], p = 0.39). In patients with stable CAD and normal treadmill exercise stress test results, the QTc interval, the Tpe interval, and the Tpe/QT ratio increased during exercise. In conclusion, it is reasonable to assume that despite the absence of inducible ischemia, the spatial dispersion of repolarization is increased during exercise, exposing these patients to increased arrhythmic risk.** **© 2011 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2011;107: 37–40)**

Coronary artery disease (CAD) is the condition most commonly associated with malignant ventricular arrhythmias and sudden cardiac death (SCD).[1] Exercise is a classic trigger of ventricular arrhythmias in this setting, although the significance of exercise-induced arrhythmias in predicting future morbidity and mortality is controversial.[2–4] Vigorous exertion increases the risk for cardiac arrest, especially in patients who are not physically active.[2] Terminal repolarization, calculated as the interval from the peak to the end of the T wave, has been related to SCD risk. A well-known pathogenetic factor for ventricular arrhythmias is the increased dispersion of repolarization, which reflects the heterogeneity rather than the total duration of repolarization.[5] In fact, the T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel electrocardiographic (ECG) indexes of arrhythmic risk that possibly correspond to the spatial dispersion of ventricular repolarization.[5–7] In this study, we sought to investigate the effects of exercise on the aforementioned ECG indexes in patients with stable CAD who underwent regular exercise stress testing.

## Methods

In this observational study, consecutive patients with stable CAD who were referred for regular treadmill exercise stress testing were screened. In addition, we checked subjects referred for exercise stress testing because of atypical chest pain or in the context of a regular checkup (control group). Exclusion criteria were recent acute coronary syndromes within the past 6 months, recent percutaneous coronary intervention or cardiac surgery, any physical disability, congestive heart failure with New York Heart Association class >II, history of channelopathies, history of syncope, presence of nonsustained ventricular tachycardia on Holter monitoring, presence of bundle brunch block, QRS duration >120 ms, presence of second- or third-degree atrioventricular block, atrial fibrillation, previous implantation of a pacemaker or a defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, thyroid dysfunction, acute and chronic infections or inflammatory diseases, renal failure, and electrolyte disturbances. All participants were able to perform normal daily activities, and their functional capacity was

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Table 1
Clinical and demographic characteristics of the patients (n = 67)

| Variable | Value |
|---|---|
| Age (years) | 62 ± 9 |
| Men | 60 (89.5%) |
| Body mass index (kg/m$^2$) | 27.4 ± 2.8 |
| Previous myocardial infarction | 38 (56.7%) |
| Diabetes | 9 (13.4%) |
| Hypertension | 26 (38.8%) |
| Congestive heart failure | 9 (13.4%) |
| Left ventricular ejection fraction | 42.9 ± 5.5 |
| Drugs | |
| β-blockers | 55 (82%) |
| ACE inhibitors/ARBs | 41 (61%) |
| Aspirin | 56 (83%) |
| Clopidogrel | 44 (66%) |
| Statins | 63 (94%) |
| Nitrates | 17 (25%) |
| Diltiazem | 2 (3%) |

Data are expressed as mean ± SD or as number (percentage).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

satisfactory, but they were not following regular exercise programs.

The participants underwent treadmill exercise stress testing according to the Bruce protocol. We analyzed subjects who successfully completed the test without clinical or ECG evidence of ischemia. Demographic, clinical, and ECG indexes of repolarization were carefully recorded. The ECG indexes were assessed at baseline in the supine position and at the peak of exercise.

Specifically, the QT and QTpeak intervals were measured manually on ECG recordings at a paper speed of 50 mm/s. QT interval was assessed as the time between the first deflection of the QRS complex and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT − QTpeak. The QT interval was measured in as many of the 12 leads as possible, while the Tpe interval was assessed in the precordial leads.[6] The Tpe interval and the Tpe/QT ratio were calculated using the corresponding values from each lead. The measurements were obtained in 3 consecutive complexes of each lead, and the resulting average value was accepted. To avoid diurnal variation, we performed the stress tests during the same time interval (from 9 to 11 AM). QT interval corrected for heart rate (QTc) was calculated using Bazett's formula ($QTc = QT/RR^{-2}$).[8] The Tpe and QTc reported values were the maximum obtained values. All measurements were performed by 1 experienced investigator unaware of the clinical characteristics of the study participants. To identify intraobserver variability, the ECG tracings of 10 randomly selected patients were reexamined 10 days after the initial evaluation. Intraobserver variation was <5%.

Continuous variables are expressed as mean ± SD or as median (25th percentile, 75th percentile) if their values were not normally distributed. The examination of normality was performed by the Kolmogorov-Smirnov test. Categorical variables are presented as absolute numbers and frequencies. Comparisons of continuous ECG variables were performed using the nonparametric Wilcoxon signed-rank test.

Table 2
Exercise stress test parameters in the group of patients (n = 67)

| Variable | Value |
|---|---|
| Heart rate at baseline (beats/min) | 66 (57, 79) |
| Heart rate at peak exercise (beats/min) | 134 (123, 146) |
| Systolic arterial pressure at baseline (mm Hg) | 130 (120, 140) |
| Diastolic arterial pressure at baseline (mm Hg) | 80 (77, 85) |
| Systolic arterial pressure at peak exercise (mm Hg) | 170 (160, 182) |
| Diastolic arterial pressure at peak exercise (mm Hg) | 84 (78, 90) |
| METs | 10.5 (9.1, 11.7) |
| Heart rate recovery, first minute (beats/min) | 20 (15, 26) |
| Heart rate recovery, second minute (beats/min) | 38 (30, 47) |
| Heart rate recovery, third minute (beats/min) | 47 (40, 56) |

Data are expressed as median (25th percentile, 75th percentile).

Table 3
Electrocardiographic repolarization parameters in patients with coronary artery disease (n = 67)

| Variable | Baseline | Peak Exercise | p Value |
|---|---|---|---|
| QT interval (ms) | 360 (320, 400) | 280 (260, 320) | <0.001 |
| QTc interval (ms) | 385 (357, 407) | 418 (381, 447) | <0.001 |
| Tpe interval (ms) | 42 (36, 60) | 78 (60, 84) | <0.001 |
| Tpe/QT ratio | 0.17 (0.14, 0.22) | 0.21 (0.16, 0.25) | 0.015 |

Data are expressed as median (25th percentile, 75th percentile).

Table 4
Electrocardiographic repolarization parameters in control subjects (n = 68)

| Variable | Baseline | Peak Exercise | p Value |
|---|---|---|---|
| QT interval (ms) | 360 (310, 390) | 270 (240, 280) | <0.001 |
| QTc interval (ms) | 406 (380, 436) | 418 (381, 447) | 0.108 |
| Tpe interval (ms) | 62 (41, 80) | 48 (40, 78) | 0.05 |
| Tpe/QT ratio | 0.18 (0.12, 0.22) | 0.16 (0.14, 0.21) | 0.39 |

Data are expressed as median (25th percentile, 75th percentile).

A 2-tailed p value <0.05 was considered significant. All analyses were performed using SPSS version 13.0 (SPSS, Inc., Chicago, Illinois).

## Results

A total of 67 consecutive patients with stable CAD successfully completed the protocol. The baseline clinical and demographic characteristics of the patients are listed in Table 1, and the exercise stress test parameters are listed in Table 2. The QTc interval significantly increased from baseline to peak exercise (Table 3). The Tpe interval and the Tpe/QT ratio were also significantly increased at peak exercise (Table 3). No significant ventricular arrhythmias were observed. In 3 patients, some premature ventricular beats were observed during the third stage of the protocol, while 1 additional patient had premature ventricular beats and bigeminy during the first 3 minutes of recovery. Heart rate recovery during the first 3 minutes is listed in Table 2.

The control group consisted of 68 patients (mean age 60 ± 11 years, 52 men, 19% with diabetes, 41% with hypertension) without known histories of CAD. These subjects successfully completed the exercise stress test protocol (METs achieved 10

[7.9, 10.9], baseline heart rate 74 beats/min [66 beats/min, 81 beats/min], peak heart rate 148 beats/min [131 beats/min, 160 beats/min]). The QTc interval did not change significantly, the Tpe interval decreased at peak exercise, and the Tpe/QT ratio did not show a significant change in this group (Table 4).

## Discussion

The results of the present study demonstrate that QTc interval, Tpe interval, and Tpe/QT ratio significantly increase at peak exercise in patients with stable CAD who complete normal treadmill exercise stress tests. It can therefore be assumed that despite the absence of inducible ischemia, the spatial dispersion of repolarization is increased during exercise, exposing these patients to increased arrhythmic risk. In contrast, subjects without history of CAD show decreases of Tpe interval at peak exercise, while the QTc interval and the Tpe/QT ratio remain unchanged.

A recent study performed in 19 healthy young volunteers showed that the QT interval shortens from the first to the last minute of exercise, while the Tpe interval does not shorten with exercise, remaining unchanged. The investigators concluded that the dispersion of repolarization remains long, even after QT shortening, and therefore may contribute to the increased risk for SCD during and after exercise.[9] No data on the Tpe/QT ratio were provided.

The Tpe interval represents a novel index of arrhythmic risk. Regardless of the controversy over whether it is a marker of transmural or global dispersion of repolarization,[6,7,10] it has been clearly associated with increased risk for malignant ventricular arrhythmias in a variety of conditions, including long-QT syndrome (acquired and congenital), short-QT syndrome, Brugada syndrome, acute ST-segment elevation myocardial infarction, and hypertrophic cardiomyopathy.[6,11–18]

The spatial dispersion of repolarization reflects the heterogeneity of repolarization, which creates voltage gradients and thus promotes ventricular arrhythmias. The Tpe interval represents a promising marker of total dispersion of ventricular repolarization (transmural, apicobasal, or global).[6] However, the Tpe/QT ratio appears to be a more sensitive arrhythmogenic index, because it remains constant despite changes in the heart rate (dynamic changes in the Tpe and QT intervals occur in a proportional and parallel fashion).[6,11,18] The Tpe/QT ratio is increased in acute myocardial infarction, in long-QT and short-QT syndromes, and in patients with Brugada syndrome with inducibility of ventricular arrhythmias during programmed ventricular stimulation.[6,18]

Taking into account the aforementioned considerations, we focused on the measurement of the novel indexes Tpe interval and Tpe/QT ratio to investigate the effects of exercise on the dispersion of ventricular repolarization in patients with stable CAD. We did not measure the older index QTc dispersion, because accumulated evidence substantiates the theory that it actually represents the dispersion of ventricular repolarization.[19]

Exercise represents a well-known triggering factor of ventricular arrhythmias in patients with CAD, mainly because of the increase in sympathetic activity and release of catecholamines.[2] Furthermore, changes in repolarization may have a specific role in this setting. In fact, instability in repolarization during exercise is a manifestation of arrhythmic vulnerability in high-risk subjects.[20] Even in healthy subjects, the terminal repolarization (Tpe), a surrogate marker of dispersion of repolarization, does not shorten with exercise, perhaps contributing to the increased risk for SCD during exercise.[9] In our study, we showed for the first time that this phenomenon is exaggerated in patients with CAD.

Some limitations are apparent. First, we must acknowledge that this was a small study, and there was a predominance of men in our population. Second, half of our patients had histories of myocardial infarction (ST-segment elevation or non-ST segment elevation). Previous myocardial infarction is a well-known marker of arrhythmic risk. Also, our patients had moderately depressed left ventricular ejection fractions. Subgroup analyses were not feasible, because of the small number of patients. Thus, our results cannot be extrapolated in patients with CAD and no previous myocardial infarctions or in patients with preserved left ventricular systolic function. Third, we did not evaluate the potential prognostic role of the exercise-induced changes of the repolarization indexes with respect to future untoward events.


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