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Behavior of the Terminal T Wave During Exercise in Normal Subjects, Patients With Symptomatic Coronary Artery Disease and Apparently Healthy Subjects With Abnormal ST Segment Depression

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The Q-T interval and apex of T wave to end of T wave (aT-eT) interval were measured by computer in four age-matched study groups at rest and during exercise to determine whether: 1) the behavior of the aT-eT interval differs in patients with myocardial ischemia when compared with normal subjects, and 2) the behavior of the aT-eT interval differs in subjects with true positive and false positive ST segment responses. Group I consisted of 57 normal subjects. Group II consisted of 41 symptomatic patients with documented coronary artery disease. A group of apparently healthy subjects with asymptomatic ST segment depression during exercise was divided into two additional groups: Group III, those without coronary artery disease; and Group IV, those with coronary artery disease. Subjects were excluded from the study if they had left ventricular hypertrophy or an intraventricular conduction defect or were taking digitalis or type I antiarrhythmic agents.

There were no significant differences in the aT-eT interval and aT-eT/Q-T ratio among the four study groups when compared at rest; however, during exercise at similar heart rates, the aT-eT interval was significantly shorter and the aT-eT/Q-T ratio significantly smaller in Groups II and IV, the subjects with coronary artery disease, than in Group I, the normal subjects. The aT-eT interval and aT-eT/Q-T ratio measurements in Group III did not differ from those in Group I at rest or during exercise.

In conclusion, the aT-eT interval and aT-eT/Q-T ratio may reflect changes in myocardial repolarization in exercise-induced ischemia and may have potential for future clinical application.

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The appearance of ST segment depression on the exercise electrocardiogram is classically regarded as the hallmark of myocardial ischemia and has been shown to be of value in identifying patients with advanced coronary artery disease (1). However, a substantial percent of symptomatic patients with significant coronary disease fail to demonstrate a diagnostic ST segment response during exercise and, thus, have a false negative response. Conversely, the exercise electrocardiogram is also commonly employed to screen asymptomatic and apparently healthy individuals for potential coronary artery disease. However, the high prevalence of false positive ST segment responses in this group severely limits the value of this screening technique.

Exercise-induced myocardial ischemia may also be manifested by alterations in the Q-T interval and T wave of the electrocardiogram, and these alterations may be independent of ST segment shifts (2–4). Unfortunately, the Q-T interval is influenced by many physiologic and pharmacologic variables that have hindered its usefulness (5,6).

We previously reported on the behavior of the terminal T wave, specifically the apex of the T wave to end of the T wave (aT-eT) interval, during exercise in normal men using computer averaging and computer quantitation techniques (7). In this study, we showed that the aT-eT interval was relatively independent of heart rate and age and that it shortened with high heart rates attained during exercise. Since the aT-eT interval appears to reflect terminal repolarization of the myocardium (4), and since this portion of the T wave may be altered by myocardial ischemia, we decided to test the behavior of the aT-eT interval prospectively in different patient subsets and compare it with the behavior of the ST segment with the following questions in

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mind: 1) Does the behavior of the aT-eT interval differ in patients with myocardial ischemia when compared with normal subjects? 2) Does the behavior of the aT-eT interval differ in subjects with true positive and false positive ST segment responses?

Methods

Subject selection. Our normal subject study group (Group I) consisted of 57 members of the Indiana State Police Force who are enrolled in longitudinal cardiovascular evaluation and maximal exercise studies at the Indiana University Medical Center. All subjects were asymptomatic for cardiac disease or cardiac-related problems at the time of their exercise test evaluation and all had remained free of cardiac disease for a minimal period of 4.5 years after the evaluation. They were taking no medications and had normal rest and exercise electrocardiograms.

Our group with symptomatic coronary artery disease (Group II) consisted of 41 patients referred to Indiana University Medical Center for evaluation of chest pain. All had significant coronary artery disease (defined as ≥75% stenosis of one or more major epicardial coronary arteries) as documented by selective coronary cineangiography and all had a normal ST-T segment on their rest electrocardiogram. Patients with congestive heart failure, left ventricular aneurysm, cardiomyopathy, valvular heart disease, left ventricular hypertrophy and major intraventricular conduction defects were excluded, as were patients taking digitalis preparations and type I antiarrhythmic drugs. Approximately two-thirds of this group were taking a beta-receptor blocking agent at the time of the study for control of angina pectoris or hypertension, or both.

The remaining study group consisted of 46 apparently healthy men with significant ST segment depression during exercise testing (defined as ≥2 mm of horizontal or downsloping ST depression during or after exercise). These subjects had no signs or symptoms of cardiovascular disease. They were all referred to our exercise laboratory from an outside occupational health clinic where they had undergone routine treadmill exercise testing as a part of a preventative health maintenance program. They were subsequently divided into two groups: Group III consisted of 24 subjects who were determined to have no manifestations of coronary artery disease either during long-term follow-up for a minimal period of 5.5 years or by normal coronary cineangiography; Group IV consisted of 22 subjects who subsequently had a documented coronary event or coronary artery disease documented by coronary cineangiographic studies during the same follow-up period. For the purpose of this study, the subjects in Groups I and II were selected from larger groups of subjects on the basis of an age and exercise heart rate that matched those of the subjects in Groups III and IV (Table 1) to ensure homogeneous groups for comparison.

Exercise testing. Treadmill exercise tests were performed on all subjects using a modified Balke protocol (8). All exercise tests were continued until the subjects attained at least 90% of their predicted maximal heart rate unless: 1) the subject developed typical angina or other limiting symptoms, such as severe dyspnea or leg fatigue; 2) ventricular tachycardia, defined as three or more consecutive premature ventricular complexes, was observed; or 3) there was a decrease in systolic blood pressure of 10 mm Hg or more during exercise. Three modified bipolar leads (CC_5, CH_6 and CM_2) were recorded during and after exercise for the purpose of ST segment analysis. However, all computed measurements of the aT-eT and Q-T intervals were derived from the CC_5 (X axis) lead. The X axis lead was continuously recorded on a frequency-modulated analog tape recorder simultaneously with an electronic time code. The time code was used to identify specific exercise intervals during subsequent playback of the X axis electrocardiographic recordings for analog to digital conversion and com-

Table 1. Comparison of Age, Exercise Variables and Number of Subjects With Coronary Cineangiography in the Four Study Groups

	Group I: Normal Subjects	Group II: CAD	Group III: AH-No CAD	Group IV: AH-CAD
No. of subjects	57	41	24	22
Mean age (range) (yr)	52.0 (39 to 63)	53.6 (39 to 66)	54.9 (42 to 62)	56.2 (41 to 62)
Exercise duration (seconds)	762.2 (± 181.0)	502.1 (± 212.2)	754.2 (± 135.4)	612.9 (± 155.8)
Mean maximal exercise heart rate (beats/min)	163.5 (± 11.6)	148.3 (± 10.9)	165.6 (±9.8)	156.4 (± 10.4)
ST depression maximal exercise (mm)	0	2.9 (±0.7)	2.4 (±0.6)	3.0 (± 1.0)
ST depression after exercise (mm)	0	1.5 (±0.3)	1.1 (±0.3)	1.2 (±0.6)
No. of subjects with coronary cineangiograms	0	41	12	19

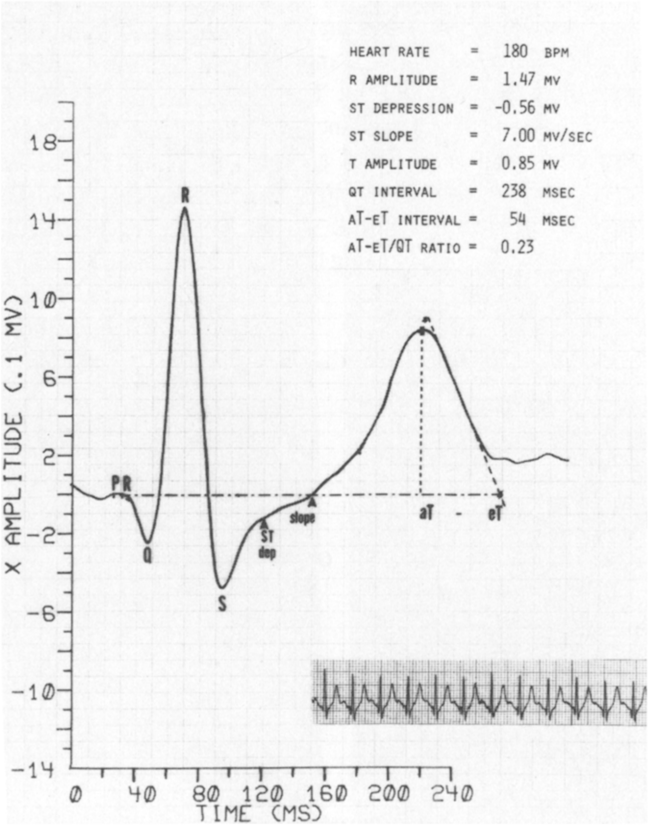
Values expressed as mean ± standard deviation. AH = apparently healthy; CAD = coronary artery disease.

puter averaging. The electrocardiographic data were digitized at a rate of 500 (12 bit) samples per channel and entered into a Nova 2-10 Data General computer for averaging of 25 consecutive normal QRS complexes for each rest and exercise interval of interest. The computer program contained algorithms for identifying and eliminating premature ventricular complexes from the averaging process.

Computer quantitation. The methods used for computer quantitation of the Q-T interval and aT-eT/Q-T ratio have been previously described (7). The T wave amplitude was also measured by computer in millivolts and the peak of the T wave was identified as the most positive point above the isoelectric line after the fiducial point. Using a moving average method of least squares lines, the slope of the T wave was defined as the least squares line that was tangent to the maximal negative slope of the T wave. For the purpose of this study, these measurements were derived from a standing rest period, submaximal exercise period I (corresponding to an exercise heart rate of 120 to 130 beats/min) and a maximal or near maximal exercise period II (corresponding to a heart rate of 145 to 160 beats/min). Enlarged computed plots of an average QRS-T complex were generated for each exercise period and were visually checked by one investigator for accuracy (Fig. 1). All data were entered into a research-oriented data management system for subsequent retrieval and analysis (9).

Statistics. Statistical analysis of the data was performed using both parametric and nonparametric tests where applicable, including an analysis of variance, Mann-Whitney U test and Student's t test for paired data.

Figure 1. A computer average of 25 consecutive QRS-T complexes plotted on a scale of 2 ms/mm is shown with computer-derived reference points for measuring T amplitude, T slope, Q-T interval and aT-eT interval.



Results

Reproducibility of the aT-eT interval in normal (control) subjects (Table 2). The stability and reproducibility of the aT-eT and Q-T interval measurements were examined in 26 of the 57 normal subjects who had undergone serial treadmill exercise testing in our laboratory within 2 consecutive years between 1979 and 1981. The Q-T and aT-eT intervals from the same rest and exercise periods were compared for each test. The respective values were remarkably similar for the two tests and there were no significant differences in the measurements over time when compared in the same individuals.

Exercise response in the study groups (Table 1). The two groups of apparently healthy subjects with abnormal ST segment depression during exercise (Groups III and IV) were compared for significant differences in age, time of onset of ST segment depression, magnitude of ST depression at maximal exercise and prevalence or duration of post-exercise depression. None of these variables proved to be significantly different in the two groups. The subjects with-

Table 2. Reproducibility of Mean aT-eT and Q-T Measurements in 26 Normal Subjects* From Two Consecutive Treadmill Exercise Tests

	Treadmill Exercise Tests†	
	No. 1	No. 2
Exercise duration (seconds)	748 ± 26	728 ± 33
Standing rest		
HR (beats/min)	74 ± 2	71 ± 2
Q-T (ms)	369 ± 5	371 ± 7
aT-eT (ms)	69 ± 2	71 ± 2
Submaximal exercise period I		
HR (beats/min)	124 ± 0.5	124 ± 0.4
Q-T (ms)	300 ± 2	300 ± 2
aT-eT (ms)	70 ± 2	69 ± 2
Submaximal exercise period II		
HR (beats/min)	143 ± 0.4	143 ± 0.4
Q-T (ms)	281 ± 2	280 ± 2
aT-eT (ms)	61 ± 1	61 ± 1
Maximal exercise		
HR (beats/min)	163 ± 3	161 ± 3
Q-T (ms)	261 ± 3	262 ± 3
aT-eT (ms)	57 ± 2	56 ± 1

Comparison of test no. 1 with test no. 2 not significant using paired t and Wilcoxon tests. All values expressed as mean ± standard deviation. * = age 52.7 ± 0.8 years (range 47 to 63); † = mean interval between tests 12.9 ± 0.3 months (range 11 to 17). Abbreviations as in Table 1.

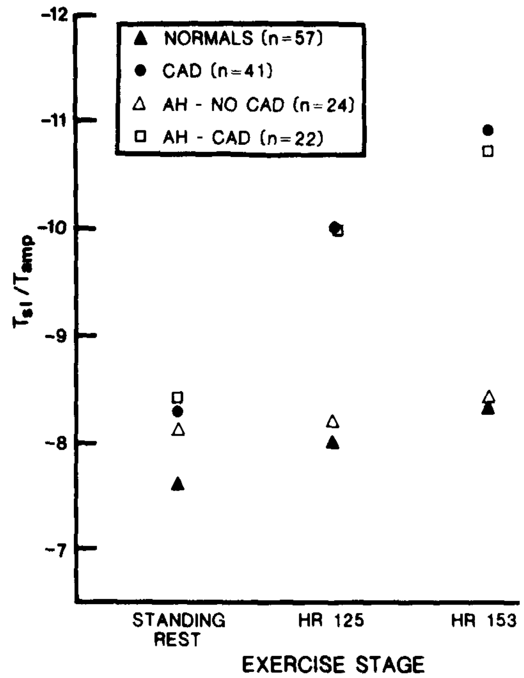


Figure 2. The ratio of T slope to T amplitude (T_{sl}/T_{amp}) is plotted against stage of exercise in the four study groups. AH = apparently healthy; CAD = coronary artery disease; HR = heart rate.

out coronary artery disease tended to exercise longer than those with coronary artery disease, but this difference did not reach the level of statistical significance.

Group II, symptomatic patients with coronary artery disease, and Group IV, apparently healthy subjects with coronary artery disease, had similar ST depression at maximal exercise and postexercise. However, Group IV subjects tended to exercise longer and achieve higher heart rates at maximal exercise as compared with Group II.

Behavior of the aT-eT interval and aT-eT/Q-T ratio (Table 3). The aT-eT interval and aT-eT/Q-T ratio were measured in all four study groups at each of the specified stages of exercise, and the values in Groups II, III and IV were compared with those in normal subjects (Group I). When measured during standing rest, at a mean heart rate of 76 beats/min, there were no significant differences in the aT-eT interval or aT-eT/Q-T ratio among the four groups. During submaximal exercise, at a mean heart rate of 125 beats/min, the aT-eT interval was significantly shorter and aT-eT/Q-T ratio significantly smaller in Group II (patients with documented coronary artery disease) and Group IV (apparently healthy subjects with ST depression and coronary artery disease) compared with corresponding measurements in normal subjects (Group I). At maximal or near maximal heart rates (mean heart rate 153 beats/min), the aT-eT interval and aT-eT/Q-T ratio measurements in Groups II and IV were significantly shorter and smaller, respectively, than similar measurements in Group I. The apparently healthy subjects without coronary artery disease (Group III) did not differ significantly from the normal subjects (Group I) at all stages of exercise. Individual data of aT-eT interval and aT-eT/Q-T ratio measurements for all four groups at rest and during exercise are provided in Figures 3 and 4.

The T wave (Fig. 2, Table 4). Since the aT-eT interval and aT-eT/Q-T ratio demonstrated an excessive shortening in patients with myocardial ischemia and coronary artery

Table 3. Comparison of aT-eT Interval and aT-eT/Q-T Ratio Measurements in Normal Subjects, Patients With Coronary Artery Disease and Apparently Healthy Subjects at Rest and During Exercise

	Group I: Normal Subjects	Group II: CAD	Group III: AH-No CAD	Group IV: AH-CAD
No. of subjects	57	41	24	22
Standing rest period (mean HR 76 beats/min)				
aT-eT (ms)‡	76.1 (± 17.1)	70.3 (± 15.1)	73.0 (± 13.7)	73.3 (± 15.2)
Q-T (ms)‡	369.4 (± 26.6)	353.3 (± 28.1)	372.4 (± 29.0)	359.3 (± 34.0)
aT-eT/Q-T‡	0.206 (± 0.041)	0.199 (± 0.038)	0.196 (± 0.037)	0.204 (± 0.039)
Exercise period I (mean HR 125 beats/min)				
aT-eT (ms)	73.8 (± 13.2)	61.9* (± 12.6)	69.7† (± 16.0)	62.9* (± 18.1)
Q-T (ms)‡	312.7 (± 14.5)	319.9 (± 18.2)	303.9 (± 30.2)	320.9 (± 19.6)
aT-eT/Q-T	0.236 (± 0.037)	0.194* (± 0.039)	0.230† (± 0.049)	0.196* (± 0.050)
Exercise period II (mean HR 153 beats/min)				
aT-eT (ms)	60.1 (± 9.5)	53.1* (± 11.3)	60.0† (± 12.1)	49.3* (± 9.1)
Q-T (ms)‡	268.3 (± 14.7)	283.9 (± 19.4)	272.7 (± 18.0)	273.8 (± 14.9)
aT-eT/Q-T	0.224 (± 0.032)	0.187* (± 0.035)	0.220† (± 0.044)	0.180* (± 0.030)

*$p < 0.001$ compared with Group I and Group II; † = not significant compared with Group I; ‡ = no significant differences among the four groups. Values expressed as mean ± standard deviation. Abbreviations as in Table 1.

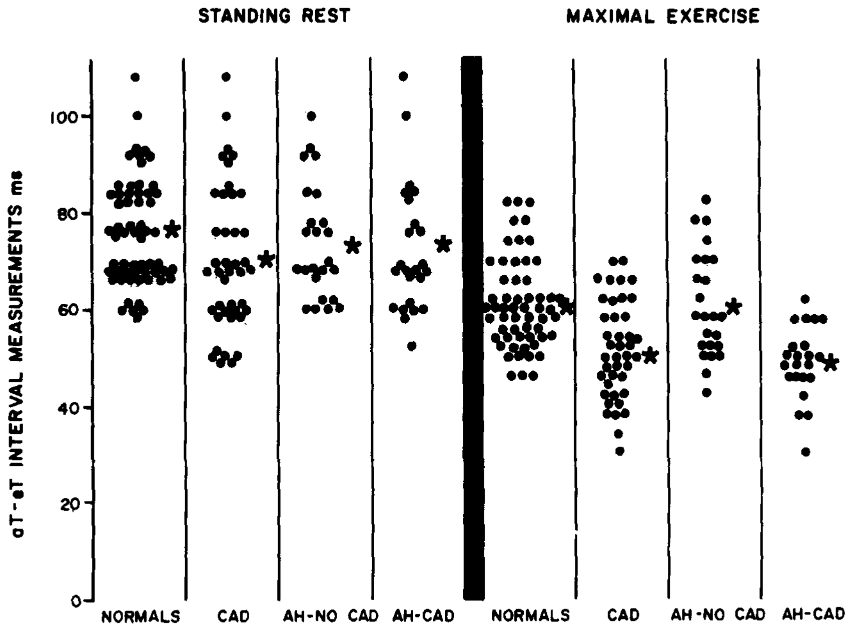


Figure 3. Individual aT-eT interval measurements in the four study groups at rest (**left**) and during exercise (**right**). * = mean value; AH = apparently healthy; CAD = coronary artery disease; normals = normal subjects.

disease, it was of interest to examine the corresponding changes in amplitude and slope of the T wave in the four study groups. The T slope, T amplitude and T slope/T amplitude ratio in the four groups were similar at rest, although the T wave amplitude in the normal group tended to be greater when compared with that in the other three groups ($p < 0.04$). With exercise, the amplitude of the T wave decreased and the T wave slope became less negative in all four groups. In the normal subjects (Group I) and the apparently healthy subjects without coronary artery disease (Group III), the percent decreases in the T wave amplitude and the T wave slope during exercise were similar and, thus, the ratio of T slope/T amplitude changed very little. In the two groups with coronary artery disease (Groups II and IV), the percent decreases in T wave amplitude were greater than were the percent decreases in T wave slope during exercise. Therefore, the ratio of T slope/T amplitude decreased significantly ($p < 0.01$), and a definite separation between subjects with and without coronary artery disease emerged (Fig. 2). The shorter aT-eT intervals observed in patients with coronary artery disease during exercise as compared with those seen in normal subjects likewise resulted from a decrease in T wave amplitude that was proportionately greater than the decrease in maximal negative T wave

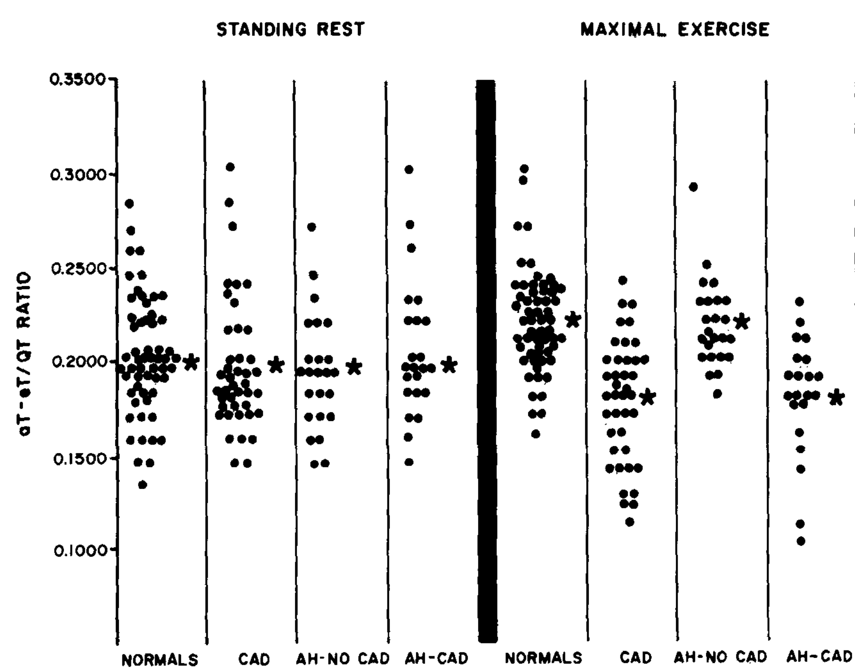


Figure 4. Individual aT-eT/Q-T ratios in the four study groups at rest (**left**) and during exercise (**right**). * = mean value; abbreviations as in Figure 3.

Table 4. Comparison of T Wave Slope, T Wave Amplitude and T Slope/T Amplitude Ratio in Normal Subjects, Patients With Coronary Artery Disease and Apparently Healthy Subjects With and Without Coronary Artery Disease at Rest and During Exercise

	Group I: Normal Subjects	Group II: CAD	Group III: AH-No CAD	Group IV: AH-CAD
No. of subjects	57	41	24	22
Standing rest (mean HR 76 beats/min)				
T slope (mV/s)	−4.5 (±1.6)	−4.0 (±2.4)	−3.4 (±1.6)	−3.8 (±2.2)
T amplitude (mV)	0.59 (±0.19)	0.48 (±0.29)	0.40 (±0.14)	0.45 (±0.25)
T slope/T amplitude	−7.6 (±0.8)	−8.3 (±2.9)	−8.5 (±1.8)	−8.4 (±0.9)
Exercise period I (mean HR 125 beats/min)				
T slope (mV/s)	−4.3 (±1.6)	−3.7 (±1.6)	−2.5 (±1.3)	−3.1 (±1.4)
T amplitude (mV)	0.54 (±0.17)	0.37 (±0.15)	0.30 (±0.12)	0.31 (±0.15)
T slope/T amplitude	−8.1 (±1.2)	−10.0 (±3.5)	−8.3 (±2.3)	−10.0 (±2.3)
Exercise period II (mean HR 153 beats/min)				
T slope (mV/s)	−4.3 (±1.9)	−3.7 (±1.8)	−2.5 (±1.4)	−2.7 (±1.2)
T amplitude (mV)	0.52 (±0.19)	0.34 (±0.16)	0.29 (±0.11)	0.26 (±0.10)
T slope/T amplitude	−8.3 (±1.3)	−10.9 (±3.9)	−8.6 (±2.8)	−10.4 (±2.7)

Abbreviations as in Table 1.

slope. Since the shortening of the Q-T interval during exercise did not differ significantly among the four study groups, the shorter aT-eT interval in patients with coronary artery disease must have been accompanied by a relative prolongation of the Q-aT interval.

In Group II, the effect of beta-receptor blocking agents on the aT-eT interval and aT-eT/Q-T ratio measurements was examined. No significant differences in these measurements were found between the patients taking a beta-receptor blocking agent and those not taking the drug; however, the numbers of patients in each subset were too small for statistical comparison.

Discussion

Changes in the ST segment during exercise have proved to be of value in identifying patients with myocardial ischemia; however, the relatively poor sensitivity and specificity of this electrocardiographic component in both symptomatic and asymptomatic patients have prompted numerous studies seeking other reliable markers of myocardial ischemia and coronary artery disease (10–15). The terminal portion of the T wave from the apex of the T wave to the end of the T wave (aT-eT interval) may be a sensitive marker of repolarization changes due to myocardial ischemia (4).

Q-T and aT-eT intervals. Lepeschkin and Surawicz (16) also demonstrated that the aT-eT interval was similar in all normal persons over a wide range of heart rates at rest. We confirmed this observation in a study of 131 normal male subjects (7). In that study, we demonstrated that the aT-eT interval shortened significantly during progressive exercise; but unlike the Q-T interval, this shortening appeared to be independent of age and at least partially independent of exercise heart rate attained. Our present study demonstrates that when subjects are matched for heart rate and age, there are no significant differences in the Q-T intervals of patients with and without ischemia.

Methodologic considerations. This study was designed to investigate the behavior of the aT-eT interval during exercise in symptomatic patients and asymptomatic, apparently healthy subjects with ST segment depression during treadmill exercise testing. The computer-quantitated aT-eT interval proved to be both a stable and reproducible measurement during serial exercise testing of 26 normal subjects. Using a modified bipolar CC_5 lead, we were able to measure the aT-eT interval by computer in more than 95% of all study subjects. Failure of the computer to correctly identify and measure the aT-eT interval was almost always due to fusion of the T and P waves at higher exercise heart rates. In our earlier studies of normal subjects, we found that an anteroposterior or Z axis lead tends to provide better separation and definition of the T and P waves at high exercise heart rates and, therefore, more consistent aT-eT interval measurements. The aT-eT interval when measured in the Z axis lead was 10 to 12 ms longer than the aT-eT interval measured simultaneously in the X axis lead. However, the changes in the aT-eT interval and aT-eT/Q-T ratio measured in the Z axis lead during exercise were similar to those measured in the X axis lead in normal subjects. The Y axis lead was too noisy and prone to changes induced by hyperventilation and heart position to be of any value. Because only a small percent of patients in our study had Z axis recordings, it was not used.

Shortening of aT-eT interval during exercise in patients with ischemia. In our patients with documented coronary artery disease (Group II) the aT-eT interval measurements shortened significantly when compared with the clinically normal subjects during exercise. The apparently healthy subjects with marked ST segment depression during exercise who had coronary artery disease likewise had shortening of the aT-eT interval measurement during exercise, which differed significantly from the normal subjects and was virtually identical to the patients with coronary artery disease (Group II). In contrast, the other subset of apparently healthy subjects with identical ST segment responses during exercise but no coronary artery disease (documented by either coronary cineangiography or long-term follow-up) had aT-eT interval responses during exercise that were indistinguishable from those in the normal subjects. These results strongly suggest that exercise-induced myocardial ischemia changes the terminal T wave in a predictable way and that these changes can be reliably measured.

The T wave changes that lead to the more pronounced shortening of the aT-eT interval in patients with coronary artery disease are complex and the underlying electrophysiologic mechanics are not understood. The exaggerated decrease in T wave amplitude and the disproportionate decrease in the maximal negative T wave slope in patients with coronary artery disease compared with normal subjects may be a reflection of the unmasking of abnormally shortened and uncancelled action potentials of the ischemic myocardium that occur during nonhomogeneous repolarization, and thus the shortened aT-eT interval emerges.

Limitations of the study. Coronary cineangiograms were not performed in our normal subjects and were available in only 50% of the apparently healthy subjects without coronary artery disease. However, we believe that our long-term follow-up evaluations in these individuals, their lack of cardiac or cardiac-related symptoms and lack of cardiac events justify including them in this study. Indeed, it is difficult to justify subjecting an entirely asymptomatic person with good exercise tolerance and ST segment depression alone on treadmill testing to the potential risks inherent in coronary cineangiography. Our results show promise, but the effects of many factors will need to be studied, such as the abnormal electrocardiographic baseline, sex, heart rate versus exercise level and effects of various drugs, specifically beta-receptor blocking and calcium channel blocking agents.

Sensitivity and specificity. Although the data demonstrate significant differences in the mean values of the aT-eT interval, aT-eT/Q-T ratio and T slope/T amplitude ratio, there is considerable overlap in the individual data to the extent that the sensitivity and specificity are only 80 and 72%, respectively, for any of these measurements to predict presence or absence of coronary artery disease. Thus, they cannot be utilized as definitive diagnostic variables in all patients. However, the aT-eT interval and aT-eT/Q-T ratio measurements may be useful in certain, well defined subgroups, particularly asymptomatic, apparently healthy subjects who demonstrate an abnormal ST segment response during treadmill exercise testing.

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