

Original Article

Validity and Predictive Value of Exercise Induced Inverted T-wave Normalization for Diagnosis of Ischemic Heart Disease

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ABSTRACT

Objectives: To evaluate the usefulness and validity of the exercise-induced T wave normalization for prediction and diagnosis of ischemic heart disease and to assess and quantify its correlation to autonomic dysfunction.

Design: A cohort study

Setting: Department of Medicine, Farwania Hospital, Kuwait

Subjects: One hundred and twenty-one patients with history of exertional chest pain with inverted T wave in the resting ECG but without history of myocardial infarction and 67 patients with T wave inversion during exercise test were included in the study.

Intervention: All patients underwent treadmill exercise ECG test and stress thallium scintigraphy in the course of their management.

Main Outcome Measures: Exercise induced T-wave

Results: There was no significant difference between

patients from both groups as regards the resting heart rate, the time of the exercise test, peak heart rate, heart rate recovery after exercise and QT dispersion after exercise, ($p = \text{NS}$). Predictive indices revealed that exercise induced T wave normalization is sensitive but not a specific indicator for prediction of ischemic heart disease, as the sensitivity was 71%, specificity = 49.2%, accuracy = 63.2%, positive predictive value = 74.4% and negative predictive value = 44.8%. A significant relation between age, smoking status, diabetes mellitus status and exercise induced T wave normalization ($p < 0.05$) was observed.

Conclusion: Exercise induced T wave normalization is a sensitive but not specific marker of exercise induced myocardial ischemia and this may be due to autonomic dysfunction with impaired parasympathetic function and unopposed sympathetic action.

KEY WORDS: exercise test, ischemic heart disease, repolarization phase

INTRODUCTION

Treadmill exercise ECG test is one of the most common non-invasive diagnostic methods used to detect ischemic heart disease^[1]. Many modifications have been proposed for improving its diagnostic accuracy^[2]. However, false positive and false negative results occur at an undesirably high rate despite all of these modifications^[3]. One of the more common ECG changes at rest among patients in whom ECG stress test is needed for diagnostic purposes is the primary T wave abnormality. One type of such abnormality persists frequently in patients with healed transmural infarction or non-transmural infarction with normal QRS duration and another type represents a common functional repolarization abnormality in persons with chest pain of uncertain etiology^[4].

Treadmill exercise ECG test still retains its clinical importance despite advances in non-

invasive diagnostic methods for detecting ischemic heart disease and the establishment of diagnostic techniques that reduce false positive and false negative rates is clinically important^[5]. However, the significance of exercise induced changes in patients who have an abnormal ECG at rest has not been fully established^[6]. The safety of the ECG stress test has been greatly enhanced by monitoring and the publications show that an abnormal ECG at rest does not contraindicate a monitored ECG stress test^[7].

The aim of this study was to prove or nullify our hypothesis that the treadmill exercise electrocardiography (ECG) induced T wave normalization is valid for diagnosis of ischemic heart disease in the presence or absence of conventional exercise induced significant ST-segment depression and that there is an association between impaired autonomic nervous function and T wave normalization.

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PATIENTS AND METHODS

Study patients:

One hundred and twenty-one patients with history of exertional chest pain with inverted T wave in the resting ECG but without history of myocardial infarction and 67 patients with T wave inversion during exercise test between February 1998 and March 2004 were included in the study. All patients were referred by their physicians to cardiologists in Farwania hospital for assessment of chest pain. All patients were evaluated clinically by looking at their medical history, physical examination, 12-leads ECG and routine laboratory investigations.

Exclusion criteria:

Patients with history of acute myocardial infarction, intraventricular conduction disturbances, strain patterns due to left ventricular hypertrophy, atrial fibrillation, mitral valve prolapse, hypertrophic cardiomyopathy, pulmonary hypertension, pericardial rub, old or recent cerebrovascular stroke, treatment with antiarrhythmic drugs that affect the repolarization interval and treatment with digoxin were excluded from the study. Exclusion was based on medical history, physical examination and 12-lead electrocardiogram to avoid confounding factors.

Transthoracic echocardiography:

Two-dimensional and M-mode echocardiography was performed for all patients in the study with the use of Toshiba Power vision and a 3.5 MHz phased array transducer. The leading edge to leading edge convention was used. Left ventricular dimensions were measured at or immediately below the tips of mitral leaflets and averaged over five heart cycles. LVM and LVM index were calculated.

Treadmill exercise ECG test protocol:

All patients underwent the exercise ECG test using standard or modified Bruce models at the baseline of the study. Resting blood pressure (measured manually by arm-cuff sphygmomanometer) was measured in supine and standing positions before the test. Patients with orthostatic hypotension (defined as a decrease of > 20 mmHg of systolic blood pressure after standing) were excluded. Resting ECG was done for all patients to exclude those with significant ST-segment changes, left bundle branch block or tachyarrhythmias.

The stress ECG test was terminated, if there was a decrease in blood pressure (> 20 mmHg), significant arrhythmias (non-sustained or sustained ventricular tachycardia), typical chest pain (test limiting angina) or > 2 mm ST-segment depression from baseline was noted. ST-segment level was

measured 60 ms after the J point in all 12 leads. Exercise induced significant ST-segment depression was defined as horizontal or downsloping ST-segment depression ≥ 1 mm in any lead.

Particular attention was given to the occurrence of normalization of negative T waves during and after exercise and to localize its site and height.

Recovery after exercise:

After achieving peak workload, the treadmill was stopped and blood pressure, heart rate, rhythm and symptoms were recorded immediately with the patient in the standing position (no cool down period). The same data were also recorded at 1, 3, 5 and 6 minutes into recovery in the supine position. Monitoring was terminated at six minutes into the recovery unless warranted by symptoms or electrocardiographic changes. Heart rate recovery was calculated as reduction in heart rate from the peak to one minute of the recovery time and a cut off value of 12 beats/minute or less was considered abnormal^[8].

Measurement of the QT dispersion:

The QT interval was measured manually by two observers using calipers from the onset of the QRS to the end of the T wave defined as the return to the TP baseline. The QT dispersion (QTd) was defined as the difference between the maximum and minimum QT interval occurring in any of the 12 ECG leads^[9].

There were two groups:

Group I: included 121 patients with exercise induced T-wave normalization.

Group II: included 67 patients without exercise induced T-wave normalization.

Stress thallium 201 scintigraphy:

All patients had undergone stress thallium scanning in the course of their management in their countries (Egypt, India and Syria). The test was considered positive if there was a reversible or fixed defect and was considered negative if there was no defect.

The patients from Group I were divided to two subgroups:

Subgroup Ia: included 90 patients with reversible thallium defects.

Subgroup Ib: included 31 patients with normal stress thallium test.

Coronary angiography:

Selective coronary cine angiography was performed in the course of their management in their countries (Egypt, India, Kuwait and Syria).

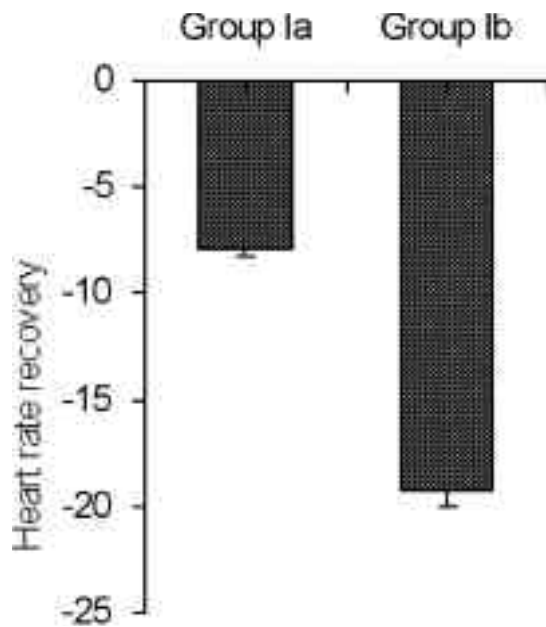


Fig. 1: Heart rate recovery after exercise ECG test in Group I

Coronary stenoses were quantified visually and luminal narrowing of > 50% was considered a hemodynamically significant coronary artery lesion.

Twenty- four hour Holter monitor and heart rate variability:

All subjects and patients of the study underwent continuous ambulatory 3-channel Holter monitoring for 24 hours. Time domain measures that were determined from normal to normal sinus beats included the mean R-R interval and its SD (SDNN), the percentage of successive R-R intervals that deviated by > 50% from the prior RR interval (p-NN50), the root mean square of successive RR interval differences (r MMD) and the SD of the average of RR intervals in all 5-minute segments of the 24-hour recording (SDANN)^[10].

Statistical analysis:

Continuous variables are summarized as a mean \pm standard deviation (SD). Comparison between two groups was performed with t-test for continuous variables and chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with exercise induced T wave normalization. The strength of the association with T wave normalization is presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables. The agreement between the two

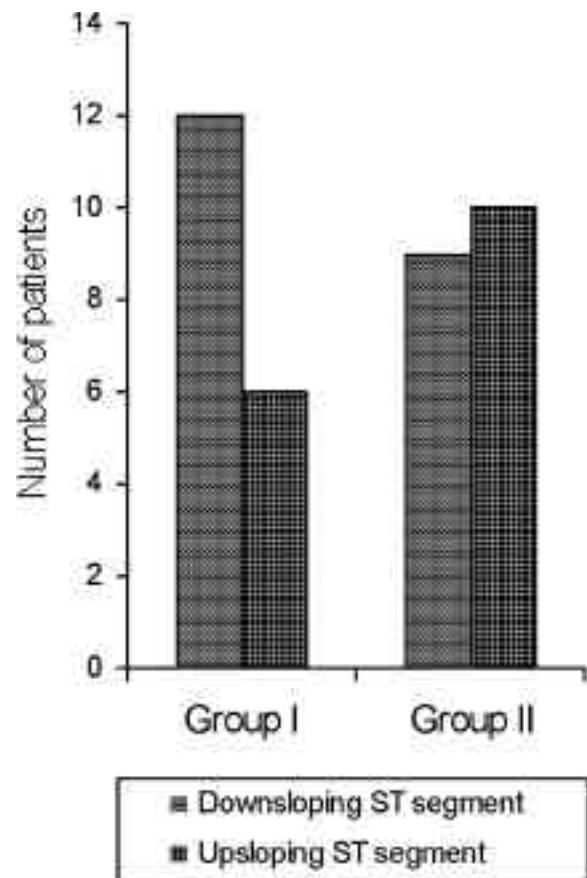


Fig. 2: Number of patients had ST segment in both Groups

observers was verified by using the method of Bland and Altman^[11]. Mean of the difference between two observers and SD were calculated to obtain limits of agreements. Upper limit of agreement = mean of difference + 2SD. Lower limit of agreement = mean - 2SD. For good agreement at least 95% of values must lie within the limits of agreement.

The validity of exercise induced T wave normalization to detect ischemic heart disease was assessed by estimating the predictive indices and Kappa coefficient to determine the overall agreement with the data obtained from the stress thallium scintigraphy.

Kappa coefficient value (k) = (Observed frequency of agreement - Expected frequency of agreement) / (Total observed - Expected frequency of agreement).

Predictive indices:

True positive (TP), true negative (TN), false positive (FP) and false negative (FN) were calculated. Sensitivity = TP / (TP + FN), specificity = TN / (TN + FP), positive predictive value = TP / (TP + TN), negative predictive value = TN / (TN + TP) and accuracy = (TP + TN) / (TP + TN + FP + FN).

Table 1: Variables of the exercise ECG test in both study groups

| Variables | Group I | Group II | p-Value |
|--------------------------------|-------------|-------------|---------|
| Exercise time (minutes) | 8.13 ± 1.36 | 9.26 ± 1.22 | NS |
| Peak heart rate (beat/min) | 158 ± 8.58 | 149 ± 10.64 | NS |
| Heart rate recovery (beat/min) | 18.4 ± 2.72 | 24.9 ± 4.07 | NS |
| QT dispersion (msec) | 6.63 ± 0.76 | 7.59 ± 0.68 | NS |

Simple linear regression (Least-square method) was used for correlation of the parameters of the study: Y (dependent variable) = $b + aX$ (independent variable), where, a = slope and b = intercept.

RESULTS

Clinical characteristics:

As regards age and gender, there was no significant difference between both groups of the study (53.31 ± 8.24 versus 48.6 ± 3.43 years, respectively, $p = NS$, 100 (82.6%) versus 60 (89.6%) males, $p = NS$ and 21 (17.3%) versus 7 (10.4%) females, $p = NS$) respectively. There was no significant difference between both groups regarding percentage of patients with history of smoking, hypercholesterolemia, hypertension and diabetes mellitus [38 (31.4%) versus 24 (35.8%) patients, $p = NS$, 32 (26.4%) versus 15 (22.2%) patients, $p = NS$, 40 (33.4%) versus 28 (41.8%) patients, $p = NS$, and 49 (40.5%) versus 30 (44.7%) patients, $p = NS$] respectively. There was no significant difference regarding the resting heart rate and blood pressure between both groups (89.25 ± 5.93 versus 78.5 ± 8.72 beat/minute and 139.37 ± 18.26 versus 128.6 ± 11.51 , $p = NS$).

Resting ECG:

Out of 90 patients who had exercise induced T wave normalization with reversible defects after stress thallium test, 69 patients had a resting ECG T-wave inversion in the chest leads V1 - V5 and 21 patients had a resting ECG T-wave inversion in the standard inferior leads III and aVF. All patients had a normal axis deviation and normal QRS complex duration. No patients had prolonged PR or QT interval.

Exercise ECG test:

There was no significant difference between both groups of the study as regards the duration of exercise ECG test, peak heart rate, blood pressure response during and after exercise and QT dispersion immediately after exercise, heart rate recovery after exercise and during recovery but there was non-significant decreased decline in the heart rate recovery after exercise in those patients than patients of Group II (18.4 ± 2.72 versus $24.9 \pm$

Table 2: Receiver operating characteristic (ROC) curve data of T wave normalization for prediction of ischemic heart disease in the patients with positive stress thallium scintigraphy

| Variables | Sensitivity % | False +ve % | AUC | POE % |
|-----------------|---------------|-------------|-------|-------|
| T-wave 2-5 mm | 75 | 39 | 0.696 | 34 |
| T-wave 5-9 mm | 79 | 34 | 0.708 | 32 |
| T-wave 10-15 mm | 82 | 28 | 0.784 | 24 |

AUC = area under curve, POE = probability of error with sensitivity 100%, mm = 0.1mv

4.07 beats, $p = NS$, Table 1). There was an impairment of autonomic function in patients from Group I with exercise induced T wave normalization and negative stress thallium test as there was a significant decreased decline in the heart rate recovery after exercise in those patients than patients from Group I with positive stress thallium test (7.9 ± 1.8 versus 19.3 ± 2.6 beats, $p < 0.05$).

There were 37 patients with a depression of ST segment at peak exercise heart rate with T wave normalization, only 18 patients had a downsloping ST segment depression > 1 mm (12 patients had T wave normalization and six patients had persistent T wave inversion and 19 patients had upsloping ST segment depression (9 patients had T wave normalization and 10 patients had persistent T wave inversion).

Stress thallium scintigraphy:

Out of 121 patients from Group I, 90 (74%) patients had a reversible defect after stress thallium test. Out of 69 (76.6%) patients with inverted T wave normalization in V2-V5, 61 patients (88%) had defects in anterior, septal and apical segments and eight patients (12%) had defects in the inferior segment. All patients with T wave inversion in lead III and aVF, had reversible defects in the inferior and posterior segments.

Coronary angiography:

Out of 61 patients with inverted T-wave normalization in V2-V5 and stress thallium defects in anterior, septal and apical segments of the left ventricle, 44 patients (72%) had significant lesions in the left anterior descending coronary artery and 17 patients (28%) had a significant lesion in the diagonal coronary artery. Out of eight patients who had inverted T wave normalization in V2-V5 and reversible thallium defects in the inferior segments, five patients (62%) had a significant lesion in the circumflex coronary artery and three patients (38%) had a significant lesion in the right coronary artery. Out of 21 patients with inverted T wave

Table 3: Stepwise logistic multivariate analysis of patients versus those without T-wave normalization as regards age, gender, smoking, hypertension, diabetes mellitus and ST depression >1mm at peak exercise heart rate

| Variables | Coefficient | p-value | 95% CI |
|--------------------------|-------------|---------|---------------|
| Age | 0.4653 | <0.05 | 1.125 - 4.091 |
| Gender | 0.2301 | NS | 0.621 - 3.505 |
| Smoking status | 0.5873 | <0.05 | 1.723 - 2.723 |
| Hypertension status | 0.1852 | NS | 0.617 - 1.795 |
| Diabetes mellitus status | 0.4852 | <0.05 | 1.420 - 2.438 |
| ST depression >1mm | 0.1914 | NS | 0.604 - 1.572 |

normalization in lead III, aVF and reversible defects after stress thallium test, nine patients (43%) had a significant lesion in the circumflex coronary artery and 12 patients (57%) had a significant lesion in the right coronary artery.

Receiver operating characteristic (ROC) curve:

ROC curve data of T wave normalization for prediction of ischemic heart disease in the patients with positive stress thallium scintigraphy revealed that there was sensitivity = 75%, false positive = 39%, area under curve = 0.696 with T wave amplitude = 2-5 mm and the probability of error was 34%. The sensitivity was 79%, false positive = 34%, area under curve = 0.708 with T wave amplitude = 6-9 mm and probability of error = 32%, but the sensitivity was increased to 82%, and there was a decrease in the false positive = 28% and the area under curve = 0.784 with T wave amplitude = 10-15 mm and there was decrease in probability of error = 24% (Table 2).

Forward stepwise logistic multivariate analysis:

Multivariate analysis revealed a significant correlation between age of the patients, smoking, and diabetes mellitus as independent variables and exercise induced T wave normalization ($R = 0.4653$, 0.573 and 0.4852 , $95\% \text{ CI} = 1.125 - 4.091$, $1.723 - 2.723$ and $1.420 - 2.438$, respectively, $p < 0.05$). However there was no significant relation as regards gender, hypertension, and presence of exercise induced ST-segment depression > 1mm and antihypertensive drugs ($p > 0.06$, Table 3, 4).

The predictive indices:

The predictive indices showed that exercise induced inverted T wave normalization is a useful marker for prediction of patients with ischemic heart disease as the sensitivity was 71%, specificity = 49.2%, accuracy = 63.8%, positive predictive value = 74.4% and negative predictive value = 44.8%.

Table 4: Stepwise logistic multivariate analysis of patients versus those without T-wave normalization as regards antihypertensive drugs

| Variables | Coefficient | p-value | 95% CI |
|--------------------------|-------------|---------|---------------|
| Beta blockers | 0.1653 | NS | 0.524 - 1.091 |
| ACE inhibitors | 0.2341 | NS | 0.227 - 1.893 |
| AR blockers | 0.3821 | NS | 0.761 - 1.590 |
| Calcium channel blockers | 0.1659 | NS | 0.228 - 1.236 |

ACE = angiotensin converting enzyme, AR = angiotensin receptors

The validity:

There was a good agreement between data of stress thallium scintigraphy and exercise induced T wave normalization with true positive = 90, true negative = 30, false positive = 31, false negative = 37 and Kappa coefficient value = 0.678 (Table 5).

Table 5: Agreement of the stress thallium 201 scintigraphy and the exercise induced T wave normalization as regards of prediction of ischemic heart disease

| | Str. thallium +ve | Str. thallium -ve | Total |
|----------------------|-------------------|-------------------|-------|
| T wave normalization | 90 | 31 | 121 |
| T-wave inversion | 37 | 30 | 67 |
| Total | 127 | 61 | 188 |

Kappa Coefficient value (k) = 0.689

Str. thallium = stress thallium test

Correlation with autonomic function variables:

There was a significant correlation between independent variables (Holter based and exercise ECG test based variables of autonomic nervous function) as X axis and dependent variable (T wave after normalization) as Y axis (Table 6).

Table 6: Correlation of the T wave after normalization as dependent variable to the Holter based and exercise ECG based variables of autonomic function as an independent variable in patients with normal stress thallium scanning, where, dependent variable = Y + independent variable x Slope, (n=31)

| Independent variables | y Intercept | Slope | r | p-value |
|---|-------------|-------|-------|---------|
| P-NN 50 (%) | 1.376 | 6.792 | 0.625 | <0.05 |
| r-MMD (msec) | 2.082 | 2.831 | 0.690 | <0.05 |
| HR response during exercise test (b/m) | 3.215 | 0.913 | 0.582 | NS |
| Decline in HR after exercise test (b/m) | 2.241 | 7.082 | 0.785 | <0.05 |

HR=heart rate

Reproducibility:

There was no significant difference in interobserver variability and intraobserver variability ($p = \text{NS}$). There was a good agreement between both observers as > 95% of the measurements were between the upper and lower limits of agreement (mean + 2SD and mean - 2SD).

DISCUSSION

Our inclusion criterion for patients in this study was the presence of an abnormal T wave at rest. This method of selection results in recruitment of patients who differ from the cross-section of patients undergoing diagnostic ECG exercise testing. In normal subjects, during exercise, the positive T wave initially shows a mild decrease of amplitude and a significant increase at peak exercise. In patients exhibiting T wave inversion on a resting electrocardiogram, the change of the polarity during effort (normalization) has been variously interpreted^[12]. Several studies have emphasized T wave normalization as a marker of myocardial ischemia^[13]. However, other investigators have discussed the clinical significance and the specificity of this sign in an unselected population, particularly in identifying transient ischemia from fixed defects. These conflicting results are probably justified by the heterogeneity of populations^[14].

The primary goal of this study was to clarify the clinical significance of T wave normalization in patients undergoing exercise stress tests for diagnostic evaluation of chest pain. The presence of resting ECG abnormalities and the fact that thallium-201 scanning defects were present in 74.4% of Group I patients strongly suggests that most patients in the study had coronary artery lesions and this was documented by coronary angiography. In this population, our results show that exercise T wave normalization represents an abnormal response to exercise even in the absence of exercise induced ST segment depression, as there was a significant ST segment depression in 12 patients only out of the patients in Group I.

In an early study, Masters^[15] considered exercise T wave normalization suggestive of myocardial ischemia if negative T waves became positive and achieved an amplitude of at least 1.5 mm. This criterion was based on the observation that T wave changes of this amplitude were accompanied by ischemic ST segment changes and it was therefore the latter finding that constituted an abnormal stress test. Urama *et al*^[16] also concluded that exercise T wave normalization was suggestive of ischemia after observing it with exercise and isoproterenol-induced angina in patients with angiographically proven coronary artery disease. However, the hypothesis that T wave normalization is diagnostic of exercise-induced ischemia had been challenged by other workers^[12].

The results of these studies suggest that exercise T wave normalization occurs from a variety of electrophysiologic mechanisms not necessarily related to the presence of myocardial ischemia. This is not surprising, since the causes of T wave normalization are complex and ill understood.

Aravindakshan *et al*^[17] postulated seven mechanisms for exercise induced changes in T wave amplitude and polarity, four of which were not dependent on the development of ischemia. In particular, they suggested that sympathetic stimulation may cause normalization of T waves. This mechanism may explain the T wave changes reported in normal subjects during exercise and isoproterenol infusion. In patients with coronary artery disease, however, different pathophysiologic mechanisms probably apply. In this setting, T wave normalization occurs predominantly secondary to previous myocardial infarction or exercise induced ischemia^[18]. Our data supported the view that T wave normalization, while not specific for the presence of underlying coronary artery disease, is a consistent sign of exercise induced ischemia, as postulated by these previous workers and there was a significant correlation between impaired autonomic nervous function and exercise induced T wave normalization in non-ischemic patients.

The previous studies revealed that the site of T wave normalization during the exercise test localized the site of the thallium-201 imaging abnormality in approximately 75% of cardiac segments analysed and similar results were also noted when patients taking digoxin were removed from analysis to exclude the effect of the drug on the ST segment and T wave^[19]. Exercise induced T wave normalization in patients with coronary artery disease represents predominantly a primary change over the affected cardiac segment rather than a reciprocal change due to abnormalities on the opposite ventricular surface. This applies to both fixed and reversible thallium-201 imaging abnormalities and suggests that more than one mechanism of T wave normalization is involved. Thus T wave normalization noted during reversible thallium 201 imaging defect may be due to an increased transmural left ventricular gradient (increased end-diastolic pressure)^[20].

Our study revealed that there was a correlation between the site of the T wave changes and thallium-201 imaging. It also suggests that T wave normalization is due to abnormalities over the affected cardiac sites in about 88% of instances and may be reciprocal to abnormalities of the opposite wall in the remaining 12%.

Limitations of this study:

1. Relatively small number of patients.
2. Single center experience.
3. Unlike ST segment changes, T-wave normalization does not occur with sufficient frequency to be useful for confirming the hypothesis of the study in the population, as out of the 1800 patients who performed exercise ECG test

in our laboratory, only 121 patients without history of old MI had exercise induced inverted T wave normalization.

4. The study is not completely blind to observers.

CONCLUSION

We conclude that exercise induced T wave normalization is a sensitive but not specific marker of exercise induced myocardial ischemia independent of the presence or absence of exercise-induced significant ST-segment depression. T wave normalization in non-ischemic patients may be due to autonomic nervous dysfunction with impaired parasympathetic function and unopposed sympathetic function.

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