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Event-Free Survival in Patients after an Acute Coronary Event with Exercise-Induced Normalization of the T-Wave

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Summary

Background: Risk stratification of patients with unstable angina or non-Q-wave myocardial infarction (MI) is an unresolved clinical problem. The prognostic value of T-wave normalization (TWN) during exercise has not been studied in this group of patients.

Hypothesis: Event-free survival in clinically stable patients after an acute coronary event without ST-segment elevation can be predicted by the presence of exercise-induced TWN.

Methods: Sixty-five patients (43 men and 22 women, mean age 62 ± 10 years) entered the study. The diagnosis of unstable angina and non-Q-wave MI was made in 40 and 25 patients, respectively. A treadmill exercise test was performed in all patients after clinical stabilization. The patients were divided into three groups: those with negative baseline T waves and exercise-induced TWN (Group 1); those with negative baseline T waves, but without TWN (Group 2); and those with positive baseline T waves (Group 3). The patients were followed up for 6 months.

Results: During follow-up, serious cardiovascular complications occurred in 15 (23%) patients. These included exacerbation of ischemic heart disease (14 patients) and acute MI (1 patient). Event-free survival was greater in patients in Group 1 (95%) than in those in Group 2 (68%, $p < 0.034$) or Group 3 (71%, NS). Among all patients studied, exercise-induced TWN was predictive of event-free survival with a sensitivity of 38% and a specificity of 93%.

Conclusions: In clinically stable patients after an acute coronary event without ST-segment elevation, exercise-induced TWN is a specific but not sensitive predictor of event-free survival after 6 months.

Key words: unstable angina, non-Q-wave myocardial infarction, T-wave normalization, prognosis, exercise test

Introduction

Acute coronary events without ST-segment elevation or new bundle-branch block are becoming an increasingly frequent cause of hospitalization in intensive care units worldwide.[1,2] Progress in pharmacologic and invasive therapy has improved the course of hospitalization; however, it has also created new problems. Most important, a dilemma exists whether to choose an invasive or conservative mode of treatment.[3–5] On the other hand, because of practical difficulties, in many cardiological centers it is still impossible to perform coronary angiography in all patients with unstable angina or non-Q-wave myocardial infarction (MI). Hence, there is a need to find new effective and reliable diagnostic methods to be applied to clinically stable patients in order to find those at risk and requiring further invasive diagnosis and therapy. One of these methods is an electrocardiographic (ECG) exercise test. However, when the interpretation of the exercise test is narrowed to analysis of changes of the ST-segment, its value is limited and has often been put into question.[6–8]

A change of the ECG T-wave deflection from negative to positive (T-wave normalization – [TWN]) is relatively often seen during an exercise test in patients after an acute coronary event.[9] The mechanisms underlying this effect are not quite clear. The possibilities include ischemia and impaired contractility or transient functional improvement of ischemic

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myocardium. Although all these factors are known to influence long-term prognosis, the actual prognostic significance of ECG exercise-induced TWN in unstable angina or non-Q-wave MI has not been studied. Therefore, the aim of the present study was to evaluate event-free survival in clinically stable patients after an acute coronary event without ST-segment elevation, with and without TWN during exercise.

Materials and Methods

Study Groups

The investigation was in accordance with the Declaration of Helsinki. In all, 290 consecutive patients, treated at the Department of Cardiology due to an acute coronary event without ST-segment elevation or new bundle-branch block, were screened for eligibility. All patients received standard pharmacologic therapy according to the guidelines of the Polish Cardiac Society. To enter the study, the patients had to fulfill the following criteria: (1) Angina [Canadian Cardiovascular Society (CCS) class III/IV] within 48 h before hospitalization; (2) ischemic ECG changes on admission (other than ST-segment elevation or a new bundle-branch block) or a documented history of ischemic heart disease (coronary angiography, myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft); (3) successful pharmacologic treatment, manifested by the absence of angina (CCS class III/IV) from the third day of hospitalization onward; (4) absence of contraindications to a submaximal exercise test, such as angina (CCS class III/IV, overt heart failure, ventricular tachycardia during hospitalization).

Of all patients screened, 65 (43 men and 22 women, mean age 62 ± 10 years) fulfilled the entry criteria and entered the study. On the basis of clinical symptoms, ECG tracings, and enzymatic changes, the diagnosis of unstable angina was made in 40 patients and non-Q-wave MI was diagnosed in 25 patients. The patients were divided into three groups: those with negative baseline T waves and exercise-induced TWN (Group 1); those with negative baseline T waves, but without TWN (Group 2); and those with positive baseline T waves (Group 3). Subsequently, the three groups were compared using statistical tests.

Exercise Test

Once clinical stabilization had been achieved, a submaximal treadmill exercise test was performed in all patients between Days 4 and 13 (on average on Day 8) of hospitalization, using Marquette Case 12 equipment (Marquette Electronics, Milwaukee, Wis., USA), according to the modified Bruce protocol. The test was considered positive in the presence of angina or in the presence of horizontal or downsloping ST-segment depression of ≥0.1 mV, measured 60 ms after the J point. T-wave normalization was recognized when a negative T wave at rest (in ≥2 leads of a 12-lead ECG, except the aVR lead, in three consecutive cardiac cycles) became positive at peak exercise (with an amplitude of ≥0.1 mV).

Follow-Up

All patients were followed up for 6 months after the date of hospitalization. The following cardiovascular complications were determined: death due to a cardiogenic cause, MI, and exacerbation of ischemic heart disease requiring hospitalization.

Statistical Analysis

All parameters were normally distributed (Kolmogorov-Smirnov test) and, therefore, parametric tests were used for statistical analysis. Analysis of variance (ANOVA) was used for comparisons between different groups with regard to various continuous parameters. When the F value permitted, the Bonferroni's multiple comparison post tests were used for comparisons between the individual groups. A chi-square test followed by Fisher's exact test was used for comparison of categorical parameters. A p value of <0.05 was considered statistically significant. All data are expressed as mean ± standard deviation.

Results

Clinical Characteristics and Exercise Test Results

There was no difference between the study groups with respect to any clinical characteristics (Table I). An ECG exer-

TABLE I Clinical characteristics of the study groups. Group 1: negative baseline T waves and exercise-induced TWN; Group 2: negative baseline T waves without TWN; Group 3: positive baseline T waves

	Group 1 n = 20	Group 2 n = 31	Group 3 n = 14	p Value
Women/men (n)	6/14	11/20	5/9	NS
Age (years)	64 ± 9	60 ± 11	62 ± 10	NS
History of smoking (n)	5	7	3	NS
Lipid levels (mg%)				
Total cholesterol	256 ± 40	213 ± 43	225 ± 60	<0.01
Triglycerides	166 ± 103	173 ± 137	167 ± 75	NS
Coexisting diseases (n)				
Diabetes	1	2	3	NS
Hypertension	7	8	6	NS
Past MI	5	9	3	NS
Medication at discharge (n)				
Aspirin	20	31	14	NS
Beta blockers	16	21	10	NS
Nitrates	9	16	8	NS
Calcium-channel blockers	3	9	2	NS
ACE inhibitors	8	8	5	NS
Antiarrhythmic agent	0	1	1	NS

Abbreviations: TWN = T-wave normalization, NS = not significant, MI = myocardial infarction, ACE = angiotensin-converting enzyme.

TABLE II Results of the exercise test in the study groups. Group 1: negative baseline T waves and exercise-induced TWN; Group 2: negative baseline T waves without TWN; Group 3: positive baseline T waves

	Group 1 n = 20	Group 2 n = 31	Group 3 n = 14	p Value
Systolic blood pressure (mmHg)				
Before exercise	136 ± 20	129 ± 20	145 ± 29	NS
At peak exercise	157 ± 24	164 ± 31	175 ± 30	NS
Heart rate (beats/min)				
Before exercise	75 ± 15	76 ± 15	77 ± 10	NS
At peak exercise	110 ± 16	108 ± 16	116 ± 17	NS
Reason for exercise termination (n)				
Pulse limit	3	1	2	NS
ST depression	12	15	11	NS
Angina	2	6	9	<0.006
Exhaustion	5	12	1	<0.04
ST depression and/or angina (n)	12	17	11	NS
Duration of exercise (s)	386 ± 210	412 ± 185	448 ± 226	NS
Maximal ST-segment depression (mm)	1.1 ± 0.8	1.0 ± 0.9	1.5 ± 0.7	NS
Sum of ischemic ST-segment depressions (mm)	6.3 ± 4.7	5.8 ± 4.4	7.5 ± 3.5	NS
Number of leads with significant ST-segment depression at peak exercise	3.0 ± 3.0	2.1 ± 2.6	3.2 ± 2.6	NS

cise test was performed in all patients studied: No serious complications were seen in any patient and the results are shown in Table II. The only significant difference between the groups was in the incidence of exercise-induced angina that was markedly greater in patients without negative T waves at baseline (Group 3). Figure 1 shows original examples of ECG recordings with (A) and without (B) TWN.

Follow-Up

The medication at discharge was similar in all groups studied (Table I). During a 6-month period of follow-up, serious cardiovascular complications occurred in 15 (23%) patients. These included exacerbation of ischemic heart disease (14 patients) and acute MI (1 patient). As shown in Figure 2, event-free survival was greater in patients with negative baseline T waves and exercise-induced TWN (95%) than in those with negative baseline T waves without TWN (68%, $p < 0.034$) or those with positive baseline T waves (71%, not significant [NS]). In contrast, there was no difference with respect to event-free survival between patients with and without exercise-induced ST-segment depression (78 vs. 76%, respectively, NS). Also, event-free survival was not significantly different between patients with and without exercise-induced angina (81 vs. 53%, respectively, NS).

Among all patients studied, exercise-induced TWN was predictive of event-free survival with a sensitivity of 38% and a specificity of 93%. Among the patients with negative baseline T waves, the sensitivity and specificity were 48 and 91%, respectively. When TWN was combined with the standard criteria for a positive exercise test (angina, ST-segment depression), it improved the overall specificity, but not sensitivity (Table III).

Discussion

The present study is the first report that evaluated the prognostic significance of ECG exercise-induced TWN in clinically stable patients after an acute coronary event without ST-segment elevation. The main finding of our study is that the highest incidence of event-free survival is seen among patients with TWN (Fig. 2). In the population studied, TWN is very specific in predicting event-free survival, but its sensitivity is relatively low. On the other hand, long-term prognosis is similar in patients with negative baseline T waves without TWN and those with positive baseline T waves. It should be noted that the use of drugs (especially beta blockers) was similar in all three groups (Table I).

The pathophysiologic mechanisms underlying TWN during exercise are still under debate. The main possibilities include acute ischemia or stunning/hibernation of the myocardium. The former is supported by the study of Elhendy *et al.*,[10] who observed T-wave changes in patients after MI undergoing dobutamine stress echocardiography. In that study, TWN was associated with perfusion defects (assessed using the isotope single-photon emission computed tomography technique), but not with impaired contractility. The ischemic etiology of TWN has also been suggested by Marin *et al.*,[11] who assessed myocardial perfusion with an isotope technique during an exercise test. However, other authors have not observed any association between exercise-induced changes in the T wave and myocardial ischemia.[12, 13] Similarly, our present results do not support such an association. Specifically, as shown in Table II, there was no difference between the groups with and without TWN with respect to exercise-induced ischemia (represented by ST-segment depression or angina). It is interesting that angina was most frequent in patients with positive T waves at rest.

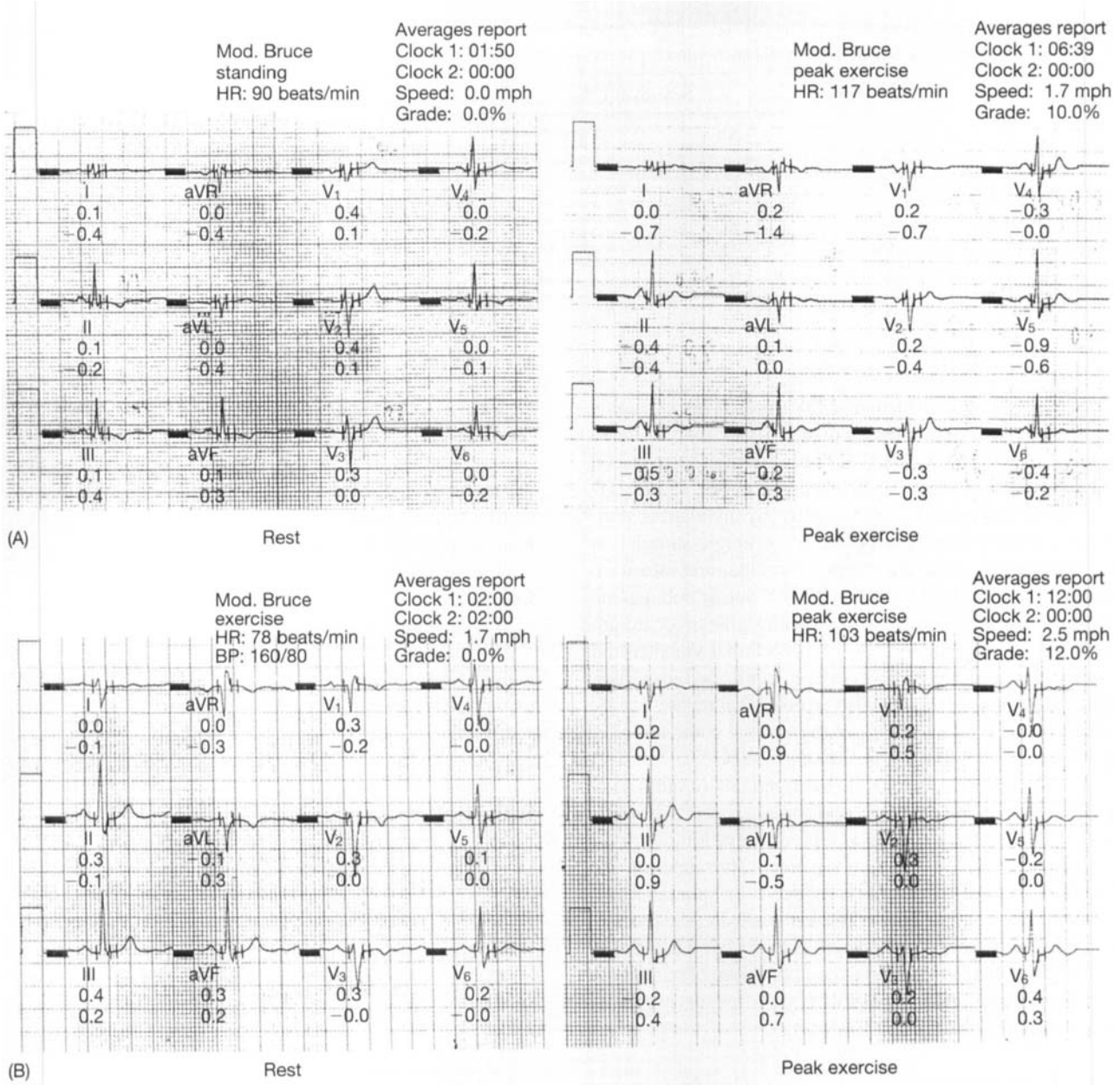

FIG. 1 Original electrocardiogram recordings at rest and at peak exercise in a patient with T-wave normalization (TWN) (A, TWN in leads II, III, aVF, V_5, V_6) and in a patient without TWN (B, negative T waves in leads aVL, V_1, V_2, V_3, V_4). Mod. = modified, HR = heart rate, BP = blood pressure.

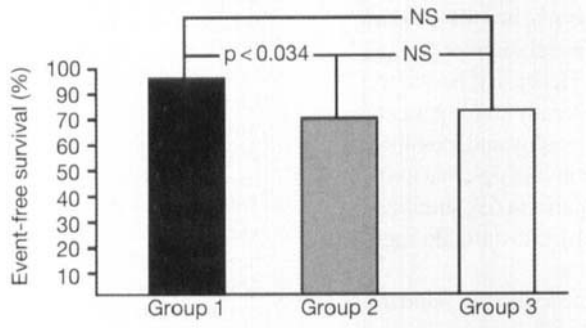

FIG. 2 Event-free survival in the study groups during a 6-month follow-up. Group 1: negative baseline T waves and exercise-induced T-wave normalization (TWN); Group 2: negative baseline T waves without TWN; Group 3: positive baseline T waves. NS = not significant.

TABLE III Sensitivity and specificity of exercise-induced ST-segment depression and angina, alone or in combination with T-wave normalization (TWN), in predicting event-free survival in all patients and in patients with negative T waves at baseline

	Sensitivity (%)		Specificity (%)	
	All patients	Patients with negative T waves	All patients	Patients with negative T waves
Absence of ST-depression	42	48	60	55
Absence of angina	82	92	53	45
Absence of ST-depression + TWN	31	44	100	100
Absence of angina + TWN	71	94	89	83

The more likely explanation of TWN seen in our patients is transient functional improvement of contractility of stunned or hibernated myocardium. It has been previously suggested that, in patients after an acute coronary event, negative T-waves on a resting ECG can be caused by myocardial stunning[14] and disappear in response to adrenergic stimulation (such as during physical exercise or dobutamine infusion). Indeed, Rambaldi *et al.*[15] observed TWN during dobutamine stress echocardiography in patients with viable myocardium after MI. An association between myocardial viability and exercise-induced TWN has also been confirmed using isotope methods.[16,17] It should also be noted that revascularization has been shown to improve myocardial contractility in patients after MI with exercise-induced TWN.[18]

Of particular relevance to the interpretation of our results are the reports of Pizzetti *et al.*[9] and Tamura *et al.*,[19] who studied the significance of TWN as a predictor of long-term recovery of contractile function in patients after anterior MI. They have found that exercise-induced[9] or spontaneous[19] TWN indicates the presence of residual perfusion and predicts functional recovery of viable myocardium after 6 months. If the same mechanism is operative in our group of patients, it may explain the greater incidence of event-free survival in patients with exercise-induced TWN (Fig. 2).

Clinical Significance

A classical ECG exercise test is commonly used in the assessment of prognosis in patients after acute non-Q-wave coronary events.[20–23] The test is positive in ~ 33% of all clinically stable patients, originally hospitalized due to unstable angina. The incidence of positive results reaches 40–50% in men, diabetics, and in patients with peripheral vascular disease or a history of coronary artery disease.[24] Hence, it is necessary to find new diagnostic parameters in clinically stable patients in order to find those requiring coronarography and, possibly, further invasive therapy. Our present results suggest that exercise-induced TWN may be used as an adjunct in risk stratification of clinically stable patients admitted due to unstable angina or non-Q-wave MI.

It should be noted that, when combined with the standard criteria for a positive exercise test (angina, ST-segment depression), TWN improved the overall specificity, but not sensitivity (Table III). Thus, it may be particularly useful in certain subpopulations of patients (e.g., women), in whom standard exercise test criteria are not sufficiently specific and have a low prognostic value. Therefore, our results require confirmation on a larger population of patients and in various clinically defined subpopulations of patients.

Conclusion

In clinically stable patients after an acute coronary event without ST-segment elevation, exercise-induced T-wave normalization is a specific but not sensitive predictor of event-free survival after 6 months.

References

1. Théroux P, Lidon R-M: Unstable angina: Pathogenesis, diagnosis and treatment. *Curr Probl Cardiol* 1993;18:159–214
2. Maggioni AP, Schweiger C, Tavazzi L, on behalf of the EARISA Investigators: The diagnostic-therapeutic processes in patients with unstable angina in Italy: Results of the EARISA registry (abstr). *Eur Heart J* 1998;19(suppl):559
3. Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC II) Investigators: Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354: 708–715
4. Yusuf S, Flather M, Pogue J, Hunt D, Varigos J, Piegas L, Avezum A, Anderson J, Keltai M, Budaj A, Fox K, Ceremużyński L, for the OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators: Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. *Lancet* 1998;352:507–514
5. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW: Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with conservative management strategy: Veterans Affairs non-Q-wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785–1792
6. Morrow K, Morris CK, Froelicher VF, Hideg A, Hunter D, Johnson E, Kawaguchi T, Lehmann K, Ribisl PM, Thomas R: Prediction of cardiovascular death in men undergoing noninvasive evaluation for coronary artery disease. *Ann Intern Med* 1993;118:689–695
7. Krone JR, Dwyer EM, Greenberg H, Miller JP, Gillespie JA, and the Multicenter Post-Infarction Research Group: Risk stratification

in patients with first non-Q- wave myocardial infarction: Limited value of the early low level exercise test after uncomplicated infarcts. *J Am Coll Cardiol* 1989;14:31–37

8. Brown KA: Prognostic value of myocardial perfusion imaging: State of the art and new developments. *J Nucl Cardiol* 1996;3: 516–537
9. Pizzetti G, Montorfano M, Belotti G, Margonato A, Ballarotto C, Chierchia SL: Exercise-induced T-wave normalization predicts recovery of regional contractile function after anterior myocardial infarction. *Eur Heart J* 1998;19:420–428
10. Elhendy A, Geleijnse L, Salustri A, van Domburg RT, Cornel JH, Arnese M, Roelandt JR, Fioretti PM: T wave normalisation during dobutamine stress testing in patients with non-Q-wave myocardial infarction. *Eur Heart J* 1996;17:526–531
11. Marin JJ, Heng MK, Sevrin R, Udhoji VN: Significance of T wave normalization in the electrocardiogram during exercise stress test. *Am Heart J* 1987;114:1342–1348
12. Aravindakshan V, Surawicz B, Allen RD: Electrocardiographic exercise test in patients with abnormal T waves at rest. *Am Heart J* 1977;93:706–714
13. Frais MA, Hoeschen RJ: Exercise-induced T wave normalization is not specific for myocardial ischemia detected by perfusion scintigraphy. *Am Heart J* 1990;119:1225–1229
14. Renkin J, Wijns W, Ladha Z, Col J: Reversal of segmental hypokinesis by coronary angioplasty in patients with unstable angina, persistent T-wave inversion and left anterior descending coronary artery stenosis: Additional evidence for myocardial stunning in humans. *Circulation* 1990;82:913–921
15. Rambaldi R, Bigi R, Curti G, Occhi G: Dobutamine-induced T wave positivisation after uncomplicated myocardial infarction: A marker of myocardial viability and higher cardiac risk. *Cardiologia* 1999;44:647–652
16. Ajisaka R, Watanabe S, Masuoka T, Yamanouchi T, Saitoh T, Toyama M, Takeda T, Itai Y, Sugishita Y: Relationship between normalization of negative T waves on exercise ECG and residual myocardial viability in patients with previous myocardial infarction and no post-infarction angina. *Jpn Circ J* 1998;62:153–159
17. Mobilia G, Zanco P, Desideri A, Neri G, Alitto F, Suzzi G, Chierichetti F, Celegon L, Ferlin G, Buchberger R: T wave normalization in infarct-related electrocardiographic leads during exercise testing for detection of residual viability: Comparison with positron emission tomography. *J Am Coll Cardiol* 1998;32:75–82
18. Schneider CA, Helmig AK, Baer FM, Horst M, Erdmann E, Sechtem U: Significance of exercise-induced ST-segment elevation and T-wave pseudonormalization for improvement of function in healed Q-wave myocardial infarction. *Am J Cardiol* 1998;82:148–153
19. Tamura A, Nagase K, Mikuriya Y, Nasu M: Significance of spontaneous normalization of negative T waves in infarct-related leads during healing of anterior wall acute myocardial infarction. *Am J Cardiol* 1999;84:1341–1344
20. Swahn E, Areskog M, Berglund U, Walfridsson H, Wallentin L: Predictive importance of clinical findings and a predischarge exercise test in patients with suspected unstable coronary artery disease. *Am J Cardiol* 1987;59:208–214
21. Butman SM, Olson HG, Gardin JM, Piters KM, Hullett M, Butman L: Submaximal exercise testing after stabilization of unstable angina pectoris. *J Am Coll Cardiol* 1984;4:667–673
22. Wicox I, Freedman B, Allman KC, Collins FL, Leitch JW, Kelly DT, Harris PJ: Prognostic significance of a predischarge exercise test in risk stratification after unstable angina pectoris. *J Am Coll Cardiol* 1991;18:677–683
23. Lindahl B, Andren B, Ohlsson J, Venge P, Wallentin L: Noninvasive risk stratification in unstable coronary artery disease: Exercise test and biochemical markers. FRISC Study Group. *Am J Cardiol* 1997; 80:40E–44E
24. Moreno R, Cantalapiedra J-L, de Sa EL, Ortega A, Portales JF, Fernandez-Bobadilla J, Lopez-Sendon J-L, Delcan J-L: Determinants of a positive exercise test in patients admitted with acute non-infarct chest pain. *Int J Cardiol* 1998;66:147–151