

Anatomic and Prognostic Significance of New T-Wave Inversion in Unstable Angina

DAVID E. HAINES, MD, DANIEL S. RAABE, MD, WALTER D. GUNDEL, MD, and
FRANS J. Th. WACKERS, MD

The significance of the development of new T-wave inversion was studied in 118 consecutive patients with unstable angina. The electrocardiograms during hospitalization in the coronary care unit were analyzed for occurrence of new T-wave inversion ≥ 2 mm and correlated with findings at coronary angiography (73 patients) and at follow-up (112 patients). Twenty-nine patients had anterior T-wave inversion. Of these, 25 patients (86%) had $\geq 70\%$ diameter reduction of the left anterior descending (LAD) artery, compared with 11 (26%) of 42 patients without anterior T-wave inversion ($p < 0.001$). The sensitivity of T-wave inversion for significant LAD stenosis was 69%, specificity 89%, and positive predictive value 86%. Two patients had T-wave inversion in the inferior leads. Both patients had significant right coronary artery disease, compared

with 18 of 55 patients without inferior T-wave inversion (difference not significant [$p = \text{NS}$]). Seventy-one patients who were treated medically had 16 ± 9 months' follow-up. Of 26 patients who had T-wave inversion, 10 (38%) had cardiac events, compared with 7 (16%) of the remaining 45 patients without T-wave inversion ($p < 0.05$). Forty-one patients who had undergone coronary bypass surgery had 19 ± 9 months' follow-up. Of 22 patients with T-wave inversion, 4 (18%) had cardiac events, compared with 2 (11%) of the remaining 19 patients without T-wave inversion ($p = \text{NS}$).

Thus, development of new T-wave inversion ≥ 2 mm in patients with unstable angina (1) is predictive of significant coronary artery stenosis, and (2) identifies a subgroup with poor prognosis when treated medically.

During hospital observation, patients with unstable angina may develop new T-wave inversion on the electrocardiogram, without associated increase and decrease of cardiac enzymes. Although transient ST-T segment changes during episodes of angina pectoris are well recognized as reflections of acute myocardial ischemia,¹⁻⁸ the significance of the gradual development of T-wave inversion associated with symptoms of unstable angina is less well understood. Recently, it has been suggested that this characteristic electrocardiographic pattern is associated with a particularly poor prognosis.⁹ The purpose of the present study was 2-fold: (1) to define the pathoanatomic correlation of new T-wave inversion in patients with unstable angina, in particular the distribution and severity of coronary artery disease; and (2) to analyze the potential prognostic implications

of this finding in medically and surgically treated patients.

Methods

Patient group: The electrocardiograms and medical records of 146 consecutive patients, discharged from the coronary care unit in the period from March 1980 to August 1982 with the diagnosis of unstable angina, were reviewed. Unstable angina was defined as new or recent (< 1 month) onset of typical angina pectoris brought on by minimal exertion or at rest, or recent exacerbation of previously stable typical exertional angina pectoris.

All patients were in the coronary care unit for at least 48 hours. Cardiac enzymes (creatinine kinase, creatine kinase isoenzymes, lactic dehydrogenase isoenzymes, and serum glutamic oxaloacetic transaminase) were obtained on admission and every 6 hours for 48 hours. No patient had enzymatic documentation of myocardial infarction (MI) according to the criteria of the New York Heart Association.¹⁰

Twenty-eight patients were excluded from further analysis: 12 patients who had had acute MI < 2 weeks before readmission to the coronary care unit, 14 patients with either complete left or right bundle branch block, and 1 patient with previous transmural anterior and inferior MI. The remaining 118 patients are the study group.

From the University of Vermont, College of Medicine, Department of Medicine, Cardiology Section, Burlington, Vermont. Manuscript received November 11, 1982; revised manuscript received April 11, 1983, accepted April 12, 1983.

Address for reprints: Frans J. Th. Wackers, MD, University of Vermont, College of Medicine, Medical Center Hospital of Vermont, Cardiology Section, Baird 7, Burlington, Vermont 05401.

Treatment groups: The patients were classified into 3 groups: Group A, 42 patients (28 men, 16 women, mean age 60 years) who underwent coronary angiography and subsequently had coronary artery bypass surgery; Group B, 31 patients (16 men, 15 women, mean age 56 years) who also underwent coronary angiography but were subsequently treated medically because findings at coronary angiography revealed either nonsurgical coronary artery disease, insignificant coronary artery disease, or normal coronary arteries; and Group C, 45 patients (34 men, 11 women, mean age 62 years) who did not undergo coronary angiography for reasons of age, resolution of symptoms after intensive medical therapy with nitrates, beta-blocking agents, and/or calcium-channel blocking drugs, or presence of underlying disease that precluded surgery. It should be emphasized that because of the retrospective nature of the present study, allocation of patients to each treatment group was not affected by the presence or absence of T-wave inversion on the electrocardiogram.

Electrocardiograms: All 12-lead electrocardiograms were obtained using standard lead placement and either a Cambridge model 3038/2S or model VS 4 electrocardiographic recorder (Cambridge Instruments, Ossining, New York). Serial electrocardiograms were obtained on admission to the coronary care unit and daily thereafter for at least 2 days. Supplemental electrocardiograms were obtained during episodes of chest pain. The electrocardiographic T-wave inversion analyzed in the present study fulfilled all of the following criteria: (1) a new finding on or after coronary care unit admission in comparison to previous electrocardiograms (patients without previous electrocardiograms for comparison were not entered in the study, unless they presented with new symptoms of unstable angina); (2) a sustained (>24 hours) electrocardiographic finding, that is, not a transient phenomenon associated with pain only; (3) ≥ 2 mm in amplitude from the isoelectric line; (4) T-wave inversion present in ≥ 2 of the anterior leads (I, aVL, V2 to V6) and/or in ≥ 2 of the inferior leads (II, III, and aVF), without evidence of previous MI in the leads analyzed.

Evidence of previous anterior MI was defined as presence of Q waves >0.04 second duration in any of leads I, aVL, and V2 to V6, and of previous inferior MI as a presence of Q wave >0.03 second duration in lead II or aVF.¹⁰

The electrocardiograms were analyzed independently by 2 observers without knowledge of coronary angiographic findings or clinical outcome. Between the 2 observers, complete agreement existed on 115 of 118 electrocardiograms. On the remaining 3, a consensus was reached.

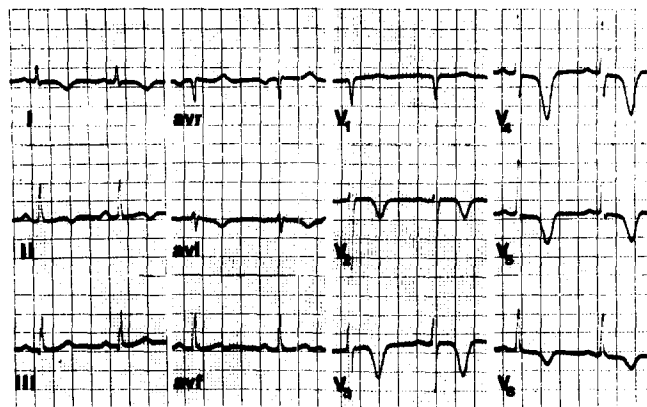


FIGURE 1. Symmetrical T-wave inversion with isoelectric S-T segment.

Electrocardiographic study groups: In the present study, the significance of the presence or absence of new T-wave inversion was evaluated only in leads without evidence of previous MI. Electrocardiographic evidence of previous anterior MI was present in 8 patients, and of previous inferior MI in 21 patients. Therefore, the anterior leads were examined in a total of 110 patients (41 in Group A, 30 in Group B, and 39 in Group C), whereas the inferior leads were examined in a total of 97 patients (34 in Group A, 23 in Group B, and 40 in Group C).

Coronary angiography: Coronary angiography was performed using the Judkins or Sones technique. Multiple projections of selective coronary angiograms were obtained. Arteriograms were analyzed by at least 2 independent experienced observers without knowledge of electrocardiographic findings. Significant stenosis of a coronary artery was defined as $\geq 70\%$ reduction of the luminal diameter determined by visual inspection. The dominant coronary artery supplying the inferior wall was noted. Left anterior descending (LAD) disease in the present study is defined as disease of the LAD or a major diagonal branch supplying blood flow to the anterior wall of the left ventricle.

Follow-up: Follow-up data on patients were obtained from private physicians' records, hospital records, or telephone interviews with the patients. MI during the follow-up period was defined as enzymatically and/or electrocardiographically documented MI. Death was assumed to be of cardiac origin if it was instantaneous, if the patient had complained of chest pain immediately before death, or if the patient died of cardiogenic shock or arrhythmia in a post-MI course.

Statistical methods: Statistical analysis was performed using the chi-square test. For analysis of series of proportions, the test for linear trend among proportions was utilized.¹¹ A p value <0.05 was considered statistically significant. Sensitivity is defined as true positives (TP) divided by false negatives (FN) + TP $\times 100$; specificity is defined as true negatives (TN) divided by TN + false positives (FP) $\times 100$; positive predictive value is defined as TP divided by TP + FP $\times 100$.

Results

Electrocardiography: Overall, new T-wave inversion ≥ 2 mm occurred in 47 (40%) of 118 patients. Twenty patients had normal electrocardiograms on admission and subsequently developed T-wave inversion. In the remaining 27 patients, T-wave inversion was either a definite new finding compared with a recent electrocardiogram (15 patients), or was considered a new finding because the symptoms of unstable angina occurred anew (12 patients). The prevalence of new T-wave inversion was not significantly different among the 3 patient treatment groups: 20 (47%) of 42 patients in Group A, 11 (35%) of 31 patients in Group B, and 16 (36%) of 45 patients in Group C ($p = \text{NS}$). Of the 110 patients without previous anterior MI, new anterior T-wave inversion occurred in 41 (37%). Of the 97 patients without previous inferior MI, new inferior T-wave inversion occurred in 6 (6%) patients. Three predominant configurations of T-wave inversion were observed, although transition from one form to another on the same or serial electrocardiograms was noted. The most common form was symmetrical inversion with isoelectric S-T segment (Fig. 1). The second form was biphasic with the inverted portion >2 mm from the

isoelectric line (Fig. 2). Finally, T-wave inversion was noted in association with S-T segment depression (Fig 3).

Coronary angiography: Of the 73 patients who underwent coronary angiography (Group A and B), 56 had $\geq 70\%$ stenosis of 1 or more coronary arteries. Twenty-seven had single-vessel, 15 had double-vessel, and 14 had triple-vessel disease. Of the remaining 17 patients, 3 patients had 50 to 70% stenosis of a single coronary artery, 2 patients had $<50\%$ stenosis of 1 vessel, and 12 patients had no evidence of coronary artery disease. Two patients had previous anterior MI, and 16 patients had previous inferior MI. The 31 patients comprising Group B were not considered for surgery for varying reasons. Fifteen patients had insignificant coronary artery disease and 8 patients had single-vessel disease only. Three patients had double-vessel disease and 5 patients had triple-vessel disease; however, they had such severe distal disease that grafting was judged not technically feasible.

New T-wave inversion and coronary artery anatomy: Thirty-one of the patients who had coronary angiography had new T-wave inversion, 27 (87%) of these had significant coronary artery disease, compared with 26 of 42 patients without new T-wave inversion ($p < 0.01$).

Anterior T-wave inversion: New T-wave inversion in the anterior leads was evaluated as a predictor of LAD disease in 71 patients without previous anterior MI. Of 29 patients with new T-wave inversion, 25 (86%) had $\geq 70\%$ stenosis of the LAD. Of 42 patients without new T-wave inversion, only 11 (26%) had significant LAD stenosis ($p < 0.0001$) (Fig. 4). For the detection of LAD disease, the anterior leads V_2 to V_6 were most important: no patients with T-wave inversion in lead I or aVL had normal anterior leads. Thus, new T-wave inversion ≥ 2 mm in the anterior leads had a positive predictive value of 86% (25 of 29), a sensitivity of 69% (25 of 36), and a specificity of 89% (31 of 35) for significant LAD disease.

Four patients who had new T-wave inversion had no significant LAD disease. Three of these had normal coronary arteries. All had resolution of their anginal

symptoms in the follow-up period without any antian-ginal medical therapy. The remaining patient had significant narrowing of the left circumflex artery. During the 28 month follow-up period, this patient continued to have anginal symptoms, despite eventual single-vessel coronary artery bypass grafting.

Inferior T-wave inversion: New T-wave inversion in the inferior leads was analyzed as a predictor for dominant right coronary artery or dominant left circumflex artery disease in 57 patients without previous inferior MI. Only 2 of 57 patients had new T-wave inversion. Both had $\geq 70\%$ stenosis of the dominant artery supplying the inferior wall of the left ventricle. In comparison, 18 of 55 patients without inferior lead T-wave inversion had comparable significant disease ($p = \text{NS}$). Thus, although new T-wave inversion in the inferior leads appears to be specific for dominant right coronary artery or left circumflex artery disease, the sensitivity is low (10%).

Amplitude of T-wave and severity of stenosis: As discussed earlier, of 42 patients without T-wave inversion in the anterior leads, 11 patients (26%) had $\geq 70\%$ LAD stenosis. In contrast, of 29 patients with ≥ 2 mm T-wave inversion in the anterior leads, 25 (86%) had significant LAD disease. Of 21 patients with ≥ 3 mm T-wave inversion, 17 (81%) had significant LAD stenosis, and 13 (81%) of 16 patients with ≥ 4 mm T-wave inversion had this finding ($p = \text{NS}$). Thus, an increased amplitude of negative T waves was not associated with higher prevalence of disease. Similarly, no correlation existed between the amplitude of negative T waves and the severity of LAD stenosis. Greater than 90% stenosis of the LAD artery occurred in 9 (66%) of 29 patients with ≥ 2 mm T-wave inversion, in 13 (62%) of 21 patients with ≥ 3 mm T-wave inversion and 12 (75%) of 16 patients with ≥ 4 mm T-wave inversion ($p = \text{NS}$).

New T-wave inversion and number of diseased coronary arteries: New T-wave inversion in the anterior leads correlates well with the presence of significant LAD disease. Of a total of 71 patients, 36 had LAD disease. Of these, 10 of 14 patients with single-vessel LAD disease, 4 of 9 patients with double-vessel disease, and 11 of 13 patients with triple-vessel disease had new T-wave inversion in the anterior leads ($p = \text{NS}$). Thus,

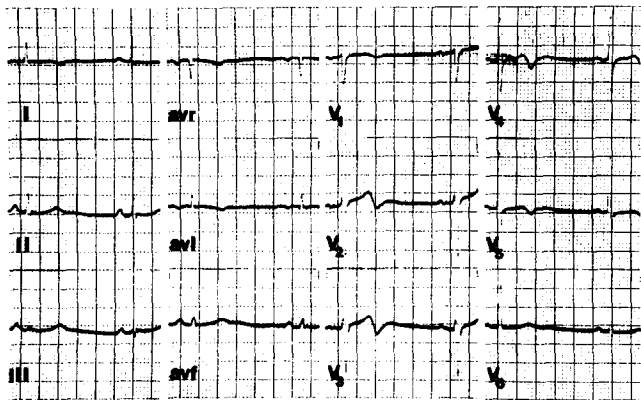


FIGURE 2. Biphasic T-wave inversion.

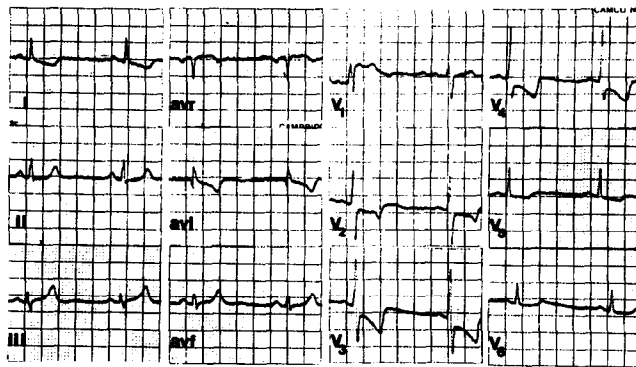


FIGURE 3. T-wave inversion associated with S-T segment depression.

the presence of new T-wave inversion is not predictive for number of vessels involved.

Follow-up: Medical treatment: A total of 76 patients (Groups B and C) were treated medically with beta-adrenergic blocking agents, nitrates, and/or calcium channel antagonists. Five patients were lost to follow-up. The remaining 71 patients had follow-up for 16 ± 9 months. Twenty-six patients had new T-wave inversion: 20 in anterior leads, 4 in inferior leads, and 2 in both anterior and inferior leads. During the follow-up period, 10 (38%) of 26 patients had either acute MI (3 patients) or cardiac death (7 patients, 27%). Of these 10 patients, 6 had anterior T-wave inversion, 3 inferior T-wave inversion, and 1 both inferior and anterior T-wave inversion. In contrast, only 7 (16%) of 45 patients without new T-wave inversion on the electrocardiogram during the hospital stay had acute MI (4 patients) or cardiac death (3 patients) during the follow-up period ($p < 0.05$) (Fig. 4). The mean length of time between coronary care unit hospitalization and cardiac event in follow-up was 6 ± 3 months in the 10 patients with new T-wave inversion, and 14 ± 6 months in the 7 patients without new T-wave inversion.

Coronary bypass surgery: Of 42 patients who underwent coronary bypass surgery (Group A), 1 was lost to follow-up and the remaining 41 patients had 19 ± 9 months (mean \pm standard deviation) follow-up. During the preoperative stay in the coronary care unit, 22 patients had new T-wave inversion (20 in anterior leads and 2 in inferior leads). Four (18%) of the patients with T-wave inversion had either MI (2 perioperative and 1 seven months after operation) or cardiac death (1 perioperative). Of 19 patients without T-wave inversion, 2 (11%) had perioperative MI ($p = \text{NS}$). The incidence of cardiac events was not different ($p = \text{NS}$) from that in patients without T-wave inversion who were treated medically.

Discussion

The results of our study indicate that, among patients with unstable angina, the electrocardiographic development of new T-wave inversion in the anterior leads

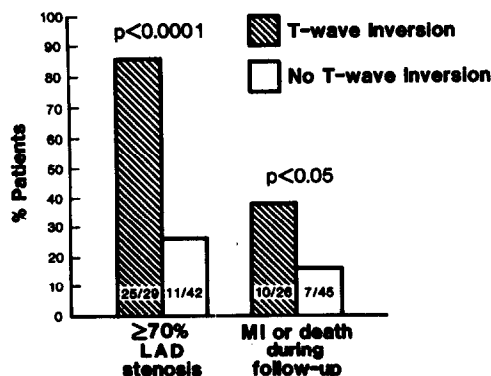


FIGURE 4. Prevalence of significant left anterior descending coronary artery stenosis and the incidence of cardiac events in patients with and without new T-wave inversion. LAD = left anterior descending coronary artery; MI = myocardial infarction.

identifies a subgroup of patients with high prevalence of significant LAD stenosis. Also, the subgroup with new T-wave inversion appears to be at high risk for subsequent MI and cardiac death. A high incidence of cardiac events occurred in patients who initially seemed to respond favorably to intensive medical treatment. Our findings corroborate in a larger group of patients, with and without new T-wave inversion, the prognostic information to be gained from the surface electrocardiogram as reported by Zwaan et al.⁹ These investigators included only patients with T-wave inversion in precordial leads V_2 and V_3 , which may in part explain the lower prevalence (18%) of T-wave inversion and the extremely high incidence (70%) of cardiac events, compared with that in our series.

Previous studies on unstable angina, as a rule, either did not separately analyze the patients with T-wave inversion and/or required electrocardiographic changes as entrance criteria to their study group.^{1-8,12} Currently, the management of individual patients with unstable angina may vary considerably in different centers. In some, immediate coronary angiography and grafting of the coronary arteries is recommended, whereas in others a more conservative attitude is taken. As a rule, the electrocardiogram is employed only as additional objective clinical evidence of myocardial ischemia when transient ST-T segment changes occur, particularly during pain. The decision to proceed with coronary angiography and subsequent coronary bypass surgery usually is predominantly based on failure of medical treatment, rather than electrocardiographic findings. The potential prognostic value of electrocardiograms in patients with unstable angina only recently has been appreciated.^{8,9,13} Our study demonstrates that not only deep negative T waves (Fig. 1) but also less impressive T-wave inversions correlate with significant stenosis of the LAD.

New negative T-wave inversion in the inferior leads occurred less frequently in our study and appeared to have less clinical value than precordial T-wave changes. Nevertheless, the 2 patients with new T-wave inversion in the inferior leads both had significant stenosis of the dominant artery supplying the inferior wall. This appears to indicate that the electrocardiographic location of new negative T-wave inversion correlates with the anatomic location of severe coronary artery stenosis. The underlying pathophysiologic mechanism of the occurrence of electrocardiographic negative T waves is incompletely understood. Reversible electrocardiographic findings associated with ischemia are often thought of as transient phenomena that resolve immediately as ischemia is diminished. Myocardial ischemia involving the subepicardial area may alter and reverse the pathway of electrical repolarization resulting in inverted T-wave morphology.^{14,15} The fact that the T-wave inversion lingers after resolution of symptoms implies structural or biochemical alteration of the myocardium.

Myocardial perfusion defects on thallium-201 scintigrams, suggesting myocardial ischemia, have been demonstrated in 40% of patients with unstable angina even during the pain-free period.¹⁶ Donsky et al¹⁷ re-

ported abnormal technetium-99m-pyrophosphate myocardial scintigrams in approximately one third of patients with unstable angina in the absence of enzymatic or electrocardiographic evidence of acute MI. Clinical-pathologic correlation in these patients demonstrated scattered foci of myocardial necrosis.¹⁸ In patients with unstable angina the distinction between severe ischemia and small nontransmural MI is an artificial one. In this light, the poor long-term prognosis of patients with new T-wave inversion in unstable angina is similar to that of patients with nontransmural MI, who have increased posthospital discharge mortality and complications.^{19,20}

Clinical implications: A recent report of a prospective study by Hultgren et al²¹ examining medical versus surgical therapy in unstable angina showed a small improvement in survival of those undergoing coronary artery bypass surgery compared with those receiving medical therapy. Early cardiac catheterization and surgery in patients with unstable angina is being advocated by some groups.^{22,23} There clearly is a need to define more precisely high-risk subgroups that could benefit most from surgery.

In patients with unstable angina, the development of new T-wave inversion on the electrocardiogram provides important prognostic information, heralding increased incidence of MI and cardiac death. Although the number of patients is relatively small and bias in patient selection cannot be excluded, the significantly lower incidence of cardiac events in patients who underwent coronary bypass surgery, compared with that in patients treated medically, suggests that this subgroup in particular benefits from a more aggressive approach. Further studies should explore results of medical versus surgical therapy in this high-risk subgroup.

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