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

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To evaluate the significance of persistent negative T waves during severe ischemia, we prospectively studied 62 patients admitted for unstable angina without evidence of recent or ongoing myocardial infarction. A critical stenosis on the left anterior descending coronary artery (LAD), considered as the culprit lesion, was successfully treated by percutaneous transluminal coronary angioplasty (PTCA). The patients were divided into two groups according to the admission electrocardiogram: T NEG group (n=32) had persistent negative T waves, and the T POS group (n=30) had normal positive T waves on precordial leads. The two groups had similar baseline clinical, hemodynamic, and angiographic characteristics. All patients underwent a complete clinical and angiographic evaluation (coronary arteriography and left ventriculography) before undergoing PTCA and 8±3 months later. Left ventricular anterior wall motion was evaluated by the percent shortening of three areas (S1, S2, and S3) considered as LAD-related segments on left ventriculograms. Before PTCA, there was no significant difference in global ejection fraction between the two groups despite a significant depression in anterior mean percent area shortening in the T NEG compared with the T POS group (S1, 44 versus 54, p<0.01; S2, 39 versus 48, p<0.01; S3, 44 versus 50, NS). At repeated angiography, the anterior mean percent area shortening improved significantly in the T NEG group (S1, from 44 to 61, p<0.001; S2, from 39 to 58, p<0.001; S3, from 44 to 61, p<0.001). This resulted in a reduced end-systolic volume (from 41±14 to 31±13 ml/m², p<0.01) and improved ejection fraction (from 61±8% to 69±10%, p<0.001) compared with baseline. The negative T waves present on the admission electrocardiogram became normalized in 31 patients (97%). There were no differences in any of the data studied between baseline and follow-up in the T POS group. We conclude that 1) the clinical syndrome of unstable angina with LAD stenosis and persistent negative T waves on precordial leads is associated with resting anterior hypokinesis that is absent in patients without this electrocardiogram pattern but who are otherwise similar; 2) successful reperfusion by PTCA of LAD can normalize the abnormal electrocardiogram and anterior regional shortening, suggesting that myocardial stunning is present in this syndrome. (Circulation 1990;82:913–921)

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During the time course of suspected myocardial infarction, the appearance of permanent abnormal Q waves on the resting electrocardiogram (ECG) is diagnostic for transmural necrosis,1,2 whereas long-standing alterations of the ST-T waves are believed to indicate non–Q wave infarction.3,4 Nevertheless, serial creatine kinase
sampling recently showed that persistent T wave inversion on the resting ECG during unstable angina may appear without evidence of necrosis.\textsuperscript{5-7} Negative T waves on precordial leads have been related to the presence of a critical stenosis on the left anterior descending coronary artery (LAD).\textsuperscript{5}

Our goal was to study the incidence of postischemic left ventricular dysfunction in this subgroup of patients with unstable angina. Specifically, the purpose of this study was twofold: 1) to evaluate the left ventricular function in patients with unstable angina associated with a critical stenosis on the LAD and persistent negative T waves in precordial leads and 2) to compare the effects of successful percutaneous transluminal coronary angioplasty (PTCA) on resting ECG and left ventricular function in these patients with patients that did not have this ECG pattern but who were otherwise similar.

**Methods**

**Patients**

We prospectively studied 62 patients who were admitted to the coronary care unit between 1984 and 1987 for primary unstable angina. Unstable angina was defined as recent episodes of angina at rest. All patients were in clinical class IIB or IIIB according to Braunwald.\textsuperscript{8} In addition, they met the following inclusion criteria: 1) no enzymatic evidence for recent or ongoing myocardial infarction from serial sampling on admission and every 6 hours for at least 48 hours; 2) significant LAD stenosis suitable for and successfully dilated by PTCA; and 3) informed consent by the patient for a follow-up study that included resting ECG examination 4--6 weeks and 6 months after admission combined with exercise thallium 201 scintigraphy and repeated angiography.

This study population was then divided into two groups according to the resting precordial ECG pattern at the time of the initial angiography. The first group (T NEG group) included 32 patients who had the following ECG pattern: 1) isolated negative T waves, symmetric or biphasic, with a negative amplitude of at least 0.2 mV; 2) isolated negative T waves in at least three precordial leads; 3) isolated negative T waves without significant ST segment or QRS changes. The second group, which served as the control group (T POS group), included 30 patients with normal positive T waves on the resting ECG. Transient ST-T changes were observed in 17 of 30 patients during or immediately after anginal episodes at rest. In 11 of the remaining 13, objective signs of myocardial ischemia had been detected by exercise testing within the last 4 weeks preceding unstable angina and subsequent hospital admission.

**Coronary Angiography**

Standard coronary angiography in multiple views was performed before PTCA, after PTCA, and at follow-up with the femoral approach. A stenosis visually estimated by two observers that reduced the internal coronary diameter by 70\% or more was considered significant. The LAD stenosis was suspected by the same two observers to be the culprit lesion in all patients after reviewing the clinical, ECG, and angiographic data. The TIMI (Thrombolysis in Myocardial Infarction) perfusion score\textsuperscript{9} was used to grade the LAD perfusion before PTCA and at final evaluation. Collateral circulation to the distal LAD was defined as partial or complete retrograde filling of the poststenotic segments.\textsuperscript{10}

**Left Ventricular Function**

Left ventricular function was evaluated by monoplane contrast ventriculography (30\° right anterior oblique view). Both premature and postpremature beats were excluded. The ventriculograms were manually outlined throughout systole and diastole in a blinded fashion by the same observer (Z.L.). Left ventricular volumes and ejection fraction were calculated by computer according to Simpson's rule after digitization of the manually traced contours. The normal range for ejection fraction determined in 12 subjects without cardiac disease was 73±6\% (mean±SD). To quantify regional wall motion during systole, we divided the left ventricular silhouette into eight segments, four anterior and four inferior, using the long axis as the reference system.\textsuperscript{11-13} The area of each segment was computed, and anterior wall motion was evaluated by the percent area shortening of the three LAD-related segments: anterobasal (S1), anterolateral (S2), and anteroapical (S3). The normal range was 66±8\% for S1, 64±12\% for S2, and 66±11\% for S3. The interobserver coefficient of variation was less than 4.4\% for the global and less than 7.9\% for the regional measurements. To avoid artifactual findings related to the reference system, the homogeneity of regional wall motion during systole was examined for all segments before and after PTCA in each group by comparing their wall motion distributions.\textsuperscript{14}

During diagnostic angiography, all patients in each group were asymptomatic and treated by oral or intravenous nitrates. The number of patients receiving \(\beta\)-blockers was not statistically different in each group (37\% in T NEG versus 43\% in T POS). No patients were given inotropic drugs. At final evaluation, all drugs were withheld 36 hours before angiography.

**Percutaneous Transluminal Coronary Angioplasty**

PTCA was performed with steerable coronary dilation systems. At least the culprit lesion on the LAD was successfully dilated in all patients. In case of multivessel coronary disease, PTCA was attempted on other stenotic vessels if technically feasible. Complete anatomic revascularization was defined as a successful PTCA of one or more vessels resulting in no remaining lesion with a stenosis diameter greater than 50\%.

Before intracoronary manipulations were started, an intravenous bolus of 10,000 IU heparin was administered. Heparin was administered thereafter...
as a 5,000-IU bolus every 30 minutes until the end of the procedure, and it was infused at the rate of 1,000 IU/hr during 12 hours. All patients were on isosorbide dinitrate before, during, and for 12 hours after the procedure. Daily medication at discharge included aspirin (100 mg), dipyridamole (225–400 mg), and a calcium antagonist (either nifedipine 30–40 mg or diltiazem 180 mg).

Follow-up

By design, all patients had accepted to undergo a complete follow-up. In the absence of recurrent symptoms, the final evaluation was performed 6 months after PTCA. In case of recurrent angina within the first 6 months, repeated angiography was performed earlier (n=11). Restenosis at repeated angiography was defined as follows: a 50–75% diameter stenosis was considered a partial restenosis and a 75% or more diameter stenosis was considered a significant restenosis. In case of significant restenosis, a second PTCA procedure was performed, and a new follow-up evaluation was performed 6 months later. The same strategy was observed in case of a second restenosis. Usually, left ventriculography was not performed at the time of repeated PTCA for restenosis. We intended to perform the final evaluation in the absence of LAD restenosis, that is, 6 months after the last successful PTCA, and did so in 59 of the 62 patients (after one PTCA in 39, two PTCA’s in 16, and three PTCA’s in four patients). Among three patients with documented restenosis, two preferred to undergo elective coronary artery bypass graft surgery, and one underwent emergency operation because repeated PTCA failed. In these three patients only (one in the T NEG and two in the T POS group), significant LAD restenosis was present at the time of final evaluation.

Exercise Testing and Thallium 201 Scintigraphy

Exercise thallium 201 scintigraphy was performed at the time of final evaluation, within 2 days before repeated angiography. The exercise test was performed on a bicycle ergometer and included quantitative analysis with three orthogonal leads as previously reported. Thallium 201 was given 1 minute before maximal exercise. Each patient underwent imaging immediately after exercise and 4 hours later. Images were obtained in the anterior, 45°, and 65° left anterior oblique projections. Perfusion defects in the anterior wall and the septum were considered as LAD related.

Statistical Analysis

Statistical analysis was performed with the χ² test to assess differences in categorical variables and paired or unpaired t test for parametric variables. The distribution of segmental area shortening before and after PTCA in each group was compared by use of the Kolmogorov-Smirnov test. A p value less than 0.05 was considered significant. Values are mean±SD.

### Table 1. Baseline Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>T NEG group (n=32)</th>
<th>T POS group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56±8</td>
<td>53±10</td>
</tr>
<tr>
<td>Women (n)</td>
<td>7 (22)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Prior inferior infarction (n)</td>
<td>3 (9)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>High blood pressure history (n)</td>
<td>6 (19)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Recent onset of angina (&lt;2 weeks) (n)</td>
<td>26 (81)</td>
<td>26 (86)</td>
</tr>
<tr>
<td>Unstable angina classification (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>21 (66)</td>
<td>22 (73)</td>
</tr>
<tr>
<td>IIIB</td>
<td>11 (34)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Time delay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From onset of symptoms to admission</td>
<td>9±7</td>
<td>12±8</td>
</tr>
<tr>
<td>From admission to angiography</td>
<td>2±3</td>
<td>2±7</td>
</tr>
<tr>
<td>From angiography to PTCA</td>
<td>6±3</td>
<td>8±5</td>
</tr>
</tbody>
</table>

Values are mean±SD where appropriate; values in parentheses are percentages.

T NEG group, patients who had isolated negative T waves on the resting electrocardiogram; T POS group, patients who had normal positive T waves on the resting electrocardiogram. PTCA, percutaneous transluminal coronary angioplasty.

Results

Baseline and Follow-up Data

As shown in Table 1, the baseline clinical characteristics of the patients were well matched in the T NEG and T POS groups. The only difference was the sex ratio because there were more women in T NEG group (22% versus 7%, p=0.05). More than 80% of the patients in each group had angina of recent onset (<2 weeks). According to the clinical classification of unstable angina, no difference was observed between the two groups because all patients were in Class IIB or IIIB. Serial sampling of cardiac enzymes was not diagnostic for recent or ongoing infarction. Three patients showed an isolated and mild rise in creatine kinase levels, which was smaller than twice the upper normal limit.

As shown in Table 2, multivessel disease was present in 41% (13 of 32) of T NEG and 43% (13 of 30) of T POS patients (NS), whereas multivessel PTCA was performed in 22% and 27% of each group, respectively (NS). TIMI grade 2 flow was present in 10 of T NEG (31%) and nine of T POS patients (30%); the remaining patients had grade 3 flow. After the first PTCA procedure, complete anatomic revascularization was obtained in 78% of T NEG and in 70% of T POS patients (NS).

There was no difference between groups in the restenosis rate considering all dilated segments (16 of 45 in T NEG versus 13 of 44 in T POS group, NS) or LAD segments only (15 of 37 in T NEG versus 10 of 35 in T POS group, NS). The flow chart of repeat angiography and PTCA is shown in Figure 1.

The first repeated angiography was performed after a mean delay of 6±2 months, and no restenosis
was present in 37, whereas partial restenosis was present in two patients. These 39 patients were free of symptoms at the time of final evaluation. A significant restenosis was observed in 23 patients (37%) at the first repeated angiography. One had multiple vessel disease and underwent surgery, whereas the 22 remaining patients underwent a second PTCA, and in one of these patients, the procedure failed. This patient underwent uneventful emergency surgery because of coronary dissection. A second repeated angiography (after successful second PTCA) was performed after a mean delay of 6±2 months in the 21 remaining patients. No restenosis was present in 16 patients, but a second restenosis was present in 5 of 21 (24%). One patient

![Flow chart depicting regimen of repeated angiography and PTCA for patient study groups.](image)

**Figure 1.** Flow chart depicting regimen of repeated angiography and PTCA for patient study groups. ANGIO, coronary angiography; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; pts, patients.
Anterior wall motion was significantly decreased in the T NEG group. The mean shortening of the LAD-related areas was 44%, 39%, and 44% compared with 54% (p<0.01), 48% (p<0.01), and 50% (NS) for the T POS group, respectively. The number of T NEG patients having a regional wall motion below the lower normal limit (mean−2SD) was 21 (66%) for S1, 14 (44%) for S2, and 15 (47%) for S3. The number of T POS patients having a regional wall motion within the normal range was 20 (67%) for S1, 21 (70%) for S2, and 20 (67%) for S3. Six months after the final PTCA, there was no difference in global ejection fraction between the two groups (69±10% in T NEG versus 65±10% in T POS). Even so, we observed a significant improvement in global ejection fraction compared with baseline in the T NEG group, increasing from 61±8% to a normal mean value of 69±10% (p<0.005). As shown in Table 3, the improvement in ejection fraction is the result of a significantly reduced end-systolic volume from 41±14 to 31±13 ml/m² (p<0.001). The anterior wall motion did not change in the T POS group with mean values remaining in the normal range. However, shortening was increased in T NEG group, reaching 61% (S1, p<0.001), 58% (S2, p<0.001), and 61% (S3, p<0.001). The distribution of all ventricular segments according to their systolic shortening before and after PTCA in each group is presented in Figure 3. This analysis demonstrates a similar distribution of area shortening before PTCA in each group, but a significant improvement in the distribution of hypokinetic segments in the T NEG group after PTCA. As shown in Table 3, angiographic evaluations were performed at similar heart rates and under similar loading conditions, except for the peak systolic pressure that was significantly higher at final evaluation in both groups. Left ventricular function analysis in the subgroup of patients without restenosis after the first PTCA (17 in T NEG and 20 in T POS group) or in patients without restenosis after multiple procedures (28 in T NEG and 26 in T POS group) or in patients with incomplete anatomic revascularization (seven in T NEG and nine in T POS group) showed results similar to the entire group. Last, the wall motion of non–LAD-related inferior and posterior segments showed no difference within or between groups.

**Resting ECG in the Group With Negative T Waves**

At final evaluation, the resting ECG leads showed reappearance of positive T waves in 97% of the patients (31 of 32) in T NEG group. Figure 4 illustrates a typical ECG and functional pattern of a patient in T NEG group before and 6 months after
successful PTCA. Among the 17 patients without restenosis after 6 months follow-up, all resting ECG tracings showed normal precordial leads. In the 18 patients with angiographic restenosis, only seven had reappearance of negative T waves at repeated angiography despite earlier normalization after PTCA.

Exercise Thallium 201 Scintigraphy

None of the 31 patients in the T NEG group showed perfusion abnormalities in the LAD-related segments (one patient did not undergo the exercise test for orthopedic reasons). Among the 30 patients in the T POS group, 27 (90%) showed normal perfusion in the LAD territory, whereas a reversible defect was found in a single patient in the absence of angina or significant restenosis. In the two remaining patients, a reversible perfusion defect was consistent with significant LAD restenosis, and these patients underwent bypass surgery. None of the patients in the T NEG and T POS groups showed fixed defects in LAD-related segments.

Discussion

The major findings of this study are twofold: 1) unstable angina associated with a critical LAD stenosis and negative T waves on precordial ECG leads is associated with resting segmental hypokinesis that is absent in patients without this ECG pattern, 2) successful reperfusion by PTCA can normalize ECG and wall motion abnormalities, suggesting that myocardial stunning is present in this syndrome.

Reversible Left Ventricular Dysfunction

Reversible myocardial dysfunction has been observed in several experimental models of both brief and repeated coronary artery occlusion followed by reperfusion. These observations allowed the development of the concept of the “stunned”
myocardium, which is myocardium characterized by the absence of myocardial necrosis according to histological analysis and by complete functional recovery over time provided full perfusion is restored. In humans, the occurrence of prolonged, but reversible, postischemic left ventricular dysfunction after transient episodes of ischemia has not been clearly demonstrated except for the subtle abnormalities in diastolic function produced by controlled ischemia during PTCA. The present data show that myocardial stunning may occur during unstable angina and that this is compatible with the pathophysiology of the syndrome.

Unstable angina is usually related to the presence of one or more severe coronary narrowings associated with spasm or intracoronary thrombus. The complex and dynamic interactions between blood constituents and the unstable plaque may lead to episodes of severe ischemia due to reduced coronary blood flow at rest. During this period, the functional outcome of the myocardium subtended by the unstable plaque will depend on the severity and the duration of these ischemic events. In the present study, all patients had a patent, but severely narrowed, LAD that was considered as the cause of repeated anginal attacks during the last days before admission.

In the T NEG group, we observed a significantly reduced anterior wall motion at rest during pain-free periods, but in the T POS group, despite a similar clinical status, regional left ventricular dysfunction was absent. This difference cannot be related to the occurrence of non-Q wave infarction in the T NEG group based on the following evidence: 1) only patients in whom serial measurements of cardiac enzyme levels were not diagnostic for myocardial necrosis were included in the present study, 2) the regional wall motion abnormalities disappeared over time as shown from repeated angiography, and these changes are unlikely related to altered hemodynamic or pharmacological conditions, 3) none of the patients had persistent defects on exercise-redistribution thallium 201 scintigraphy, suggesting the absence of scar. Therefore, the difference in ECG and functional pattern between the groups is likely related to the number, the severity, and the duration of the ischemic events having occurred before diagnostic evaluation and treatment.

According to experimental studies, postischemic left ventricular dysfunction is expected to normalize provided myocardial blood flow is restored. Perfusion was normalized in all patients by PTCA based on the absence of residual LAD stenosis in 92% of patients and the TIMI flow evaluation at final repeated angiography. In addition, the exercise thallium 201 perfusion studies showed normal tracer distribution in LAD-related segments in 95% of patients. Our observations are consistent with earlier studies showing improved wall motion after unstable angina with either PTCA or surgery as a revascularization technique. Although no data are available on the natural history of such dysfunction in the absence of revascularization, spontaneous or drug-induced normalization can be expected in some cases. Indeed, Nixon et al observed wall motion abnormalities by echocardiography even during pain-free periods in some patients with unstable angina. Several days were needed for normalization of regional function under medical treatment. In any case, the recovery of regional hypokinesis confirms retrospectively that the initial dysfunction was related to myocardial stunning.

**Resting ECG Abnormalities**

Negative T waves in the anterior chest leads in the setting of unstable angina or impending myocardial
infarction are suggestive of extensive ischemia of the anterior wall and are usually considered as indicative of limited subendocardial infarction.\textsuperscript{3,4} However, recent studies demonstrated that new T wave inversions may develop during unstable angina in the absence of any other evidence of myocardial necrosis.\textsuperscript{5-7} The underlying pathophysiology is incompletely understood. Severe ischemia may alter and reverse the pathway of electrical repolarization resulting in inverted T wave morphology.\textsuperscript{25} One may speculate that the ischemic alterations leading to reversible mechanical dysfunction also interfere with electrical depolarization and repolarization, leading to an electrophysiological correlate of functional stunning. Clinical evidence of reversible electrocardiographic and mechanical dysfunction resulting from transient ischemia has been provided by Bate- man et al.\textsuperscript{26} They reported the appearance of Q waves and regional wall motion abnormalities during intense ischemia, followed by gradual reversal of both electrical and contractile abnormalities on relief of ischemia.

\textbf{Limitations of the Study}

Our findings are based on the comparison of left ventricular function in two different groups of patients before and after PTCA. The assessment of regional function is a notoriously difficult problem. The use of a fixed reference system may be criticized because it increases the probability of detecting changes in segmental area shortening that are related to a displacement of the reference point. Therefore, we used the method proposed by Jeppson et al.,\textsuperscript{14} which analyses the behavior of the entire population of segments, regardless of their location in the ventricle. This procedure avoids errors related to the movement of the heart within the chest and to the displacement of the reference system. This approach confirmed the significant improvement in the distribution of hypokinetic segments in the T NEG group.

It is difficult to exclude any influence of medications on ventricular function analysis. We attempted to standardize the drug regimen in both groups of patients, as far as was permitted by their clinical status. During the initial evaluation, \(\beta\)-blockers were required by the same proportion of patients in the T POS and T NEG groups, whereas all patients were receiving nitrates. During the follow-up evaluation, all drugs were withheld for 36 hours in both groups. As shown in Table 3, we observed no differences between groups in the hemodynamic data during the initial or the repeated angiography. The slightly higher ventricular systolic pressures in both groups at 6 months could reflect the withdrawal of all drugs compared with the initial angiogram. Thus, we think that the observed effect cannot be attributed to altered hemodynamic or pharmacological conditions but rather reflect the consequences of ischemia and its subsequent recovery.

Coronary anatomy was visually assessed by two observers unaware of the ECG pattern. The culprit LAD stenoses were estimated greater than 70\% in diameter in both groups, and none of the vessels was totally occluded. The distal flow was evaluated according to the TIMI criteria. No differences were observed between T POS and T NEG groups. It is possible that subtle differences in stenoses severity or geometry could be detected by quantitative analysis of the coronary angiograms.

Finally, more than 40\% of patients in both groups had multivessel disease. In these patients, part of the abnormalities in left ventricular function could be related to changes in non-LAD segments. However, a complete revascularization was achieved in the same proportion of patients in both groups, and results similar to those for the entire group were found in patients with incomplete revascularization. The wall motion of non-LAD-related inferior and posterior segments showed no difference within or between groups. These data confirm that unstable angina in selected patients with multivessel disease can be managed by PTCA of the culprit lesion as also shown by others.\textsuperscript{27,28}

\textbf{Clinical and Prognostic Implications}

de Zwaan and colleagues\textsuperscript{5} showed that among patients with unstable angina, those with precordial negative T waves have a poor prognosis in the absence of surgical revascularization. This observation was confirmed by Haines et al.\textsuperscript{26} who reported 38\% of infarction and 27\% of death after a mean follow-up of 16 months, and by Ganborg et al.\textsuperscript{7} reporting 17\% of infarction and 24\% of death after a mean follow-up of 31 months. In the present study, revascularization was successfully achieved by PTCA and repeated procedures when needed. Remodeling of the unstable plaque by PTCA seemed to favorably alter the clinical outcome of our patients. Such strategy resulted in excellent medium-term prognosis, probably similar to the results of bypass surgery in patients with unstable angina.\textsuperscript{29}

\textbf{Acknowledgments}

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\textbf{References}


**KEY WORDS** unstable angina, stunned myocardium, PTCA
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.

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