Exercise-Induced ST-Segment Depression in Patients Without Restenosis After Coronary Angioplasty
Relation to Preprocedural Impaired Left Ventricular Function

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Background  ST-segment depression during exercise testing is frequently observed in the absence of restenosis after coronary angioplasty.

Methods and Results  We studied the determinants of this phenomenon in 70 consecutive patients with unstable angina related to a single left anterior descending coronary artery lesion who had successful angioplasty without restenosis (<50% stenosis by quantitative angiography). We compared preangioplasty clinical, angiographic, and hemodynamic variables in the group with positive (ExT Pos, n=35; ST depression, 2.3±0.9 mm) and negative (ExT Neg, n=35; ST depression, 0.3±0.5 mm) results on exercise testing at follow-up angiography. At this time, minimal lumen diameter (1.7±0.4 mm) and mean residual stenosis (34±11%) in the ExT Pos group were not significantly different from the values (1.9±0.5 mm, 38±10%) in the ExT Neg group. Before angioplasty, the ExT Pos group had a lower ejection fraction (63±8% versus 68±9%, P<.05), more marked anterior hypokinesis estimated by the extent of anterior wall contraction on quantitative ventriculography (P<.05), and a greater end-systolic volume (30±11 versus 25±9 mL/m², P<.05) than the ExT Neg group. At follow-up angiography, regional anterior wall motion was normal in 68 patients (97%). Anterior hypokinesis before angioplasty was strongly associated (P<.01) with a positive exercise test at control (71% compared with 31% in patients with normal wall motion before angioplasty).

Conclusions  In the absence of significant epicardial stenosis after angioplasty, ST-segment depression is strongly associated with the presence of preprocedural regional ventricular dysfunction that has recovered at follow-up angiography. (Circulation. 1994;90:148-155.)

Key Words  • restenosis • contractility • angioplasty • exercise testing

Exercise-induced ST-segment depression occurring in patients with atherosclerotic obstructive coronary disease is considered to be related to exercise-induced myocardial ischemia. However, when exercise testing is performed in patients who have successfully undergone percutaneous transluminal coronary angioplasty for a single epicardial coronary stenosis, significant ST-segment depression may occur in the documented absence of restenosis1; such a response is frequently designated as false-positive response. The pathophysiological significance of ST-segment depression in this context is not clear, although many possible explanations have been proposed.2,3

It was recently shown that the persistence of ST-segment depression on exercise testing in the absence of restenosis after angioplasty performed in patients who had stable angina and one-vessel disease was not related to an abnormality of vasomotor response at the dilated site. On the basis of these observations, El-Tamimi et al4 suggested that ST-segment depression in this setting might be related to functional alterations in small coronary vessels.

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in the subgroup of patients in whom no significant ST-depression occurred on exercise (ExT Neg group).

Patients
We identified 70 consecutive patients (55 men and 15 women) who between January 1987 and September 1991 underwent successful angioplasty of an isolated proximal (before the origin of the first large septal perforating branch) or middle (between the origin of the first large septal perforating branch and the origin of the second diagonal branch) left anterior descending stenosis and who at angiographic follow-up 6 months after the last angioplasty procedure had not developed restenosis as assessed with use of quantitative coronary angiography. Unstable angina was defined according to the criteria proposed by Braunwald; all the patients were in class B. The time delay between angioplasty and the final follow-up angiographic evaluation varied depending on whether the occurrence of restenosis necessitated the performance of repeated procedures. Thirty-seven patients had undergone one angioplasty; the remainder had undergone two (18 patients), three (7 patients), or four (8 patients) procedures.

Twenty-eight other patients who underwent angioplasty during the same period and fulfilled the criteria outlined above were excluded from the study because information relating to one or more of the variables studied was unavailable or uninterpretable. These included 18 patients in whom the ventriculogram before or after angioplasty was unsuitable for quantitative analysis due to the occurrence of multiple extrasystoles, 10 patients in whom the exercise test was uninterpretable because it was submaximal or was taking medication that is known to render the interpretation of the exercise test unreliable.

Exercise Testing
All the patients had a standard maximal Bruce protocol exercise test. All the tests were performed with use of a computerized exercise-ECG system (Case 12, Marquette Electronics) after antianginal medication had been discontinued for more than 48 hours and within 2 weeks of the follow-up angiogram that demonstrated the absence of restenosis.

ST-segment depression was considered significant if 0.1 mV or more of horizontal or downsloping ST-segment depression measured 0.06 second after the J point occurred compared with the rest baseline value. The rate-pressure product (heart rate x systolic blood pressure) was calculated at rest, at 1-mm ST-segment depression for (positive tests only), and at peak exercise.

Quantitative Coronary Angiographic Evaluation of Angioplasty Procedure
Coronary angioplasty was performed according to the standard technique in our laboratory, as previously described. Angiograms were performed in at least two projections before angioplasty and immediately after angioplasty. Measurements were performed on end-diastolic frames from angiograms obtained 2 minutes after the intracoronary administration of isosorbide dinitrate (2 mg) with use of the CAESAR (Computer-Assisted Evaluation of Stenosis and Restenosis) system. The validation of this system and the interobserver and intraobserver variations of measurements obtained under routine clinical conditions have been previously reported. All the measurements were performed by one observer who was unaware of the design of the study. A procedure was considered to be successful if the residual stenosis at the dilated site, immediately after the procedure, was <50% without major complication. Restenosis was defined as the recurrence of >50% narrowing at the dilated site on follow-up angiography. By definition, all the study patients had successful procedures without restenosis on the follow-up angiogram performed after the last angioplasty procedure.

Quantitative Evaluation of Global and Regional Left Ventricular Function

Hemodynamic Variables
Ventricular function was evaluated on single-plane right anterior oblique projection (30°). The left ventricular contours on end-systolic and end-diastolic frames were manually traced by one blinded observer and then digitized. The left ventricular end-systolic volume index (LVESVI, mL/m²), left-ventricular end-diastolic volume index (LVEDVI, mL/m²), and ejection fraction (EF, percent shortening) were calculated according to the area-length method, with use of the formula described by Kennedy et al. Segmental wall motion was measured with the radial method, using a center located at 69% of a line joining the upper edge of the aorta to the left ventricular apex at end systole. A regional wall motion index (RMI, percent shortening) was calculated for each segment with use of the following formula: RMI = 100 x (end-diastolic radius minus end-systolic radius)/end-diastolic radius (Fig 1).

To compare values for regional anterior and apical wall function before angioplasty with values at follow-up angiography, we used the values for the second (RWM₂), fourth (RWM₄), and sixth (RWM₆) radial segments as an index of anterior wall function and the values for the eighth (RWM₈) and 10th (RWM₁₀) radial segments as an index of apical function. The normal range for EF and for each of the RWMs was calculated using ventriculograms performed during routine coronary angiography in 30 subjects with atypical chest pain who had no evidence of coronary artery disease or other cardiovascular pathology. The normal range for EF was 71±7%. The normal range for each of the five RWMs studied was RWM₂, 48±12%; RWM₄, 56±13%; RWM₆, 55±13%; RWM₈, 51±13%; and RWM₁₀, 42±14%. In the study population, the wall motion index for an individual segment was considered to be normal if the value lay within 2 SD of the equivalent mean value in the control population. Anterior wall function was considered to be hypokinetic if the wall motion indexes for two or more of the five segments studied lay ≥2 SD below the normal range. The baseline values for left ventricular diastolic pressure (LVDP, mm Hg), left ventricular systolic pressure (LVSP, mm Hg), and aortic diastolic pressure (AoDP, mm Hg) were calculated before injection of contrast as the mean of 10 consecutive cycles with use of a computerized system (HEMO-TRACE 3).

Statistical Analysis
Values are given as mean±SD. The data were initially analyzed with ANOVA for repeated measures. If significant differences were detected, comparisons within groups were performed with use of paired Student’s t tests. Between-group comparisons were performed with use of unpaired Student’s t tests. Differences between proportions were assessed by χ² analysis. The statistical analyses were performed by the Department of Biostatistics (University of Lille) on SASS software (version 6.09). A value of P<0.05 was considered to indicate statistical significance.

Results

Clinical and Demographic Data
Mean age and the distribution of risk factors for coronary disease did not differ significantly in patients who had positive (ExT Pos group, n=35) or negative (ExT Neg group, n=35) results on exercise testing (Table 1). The mean interval from the onset of symptoms to the angioplasty procedure, the mean time from angioplasty to the final follow-up angiogram that documented the absence of restenosis, and the mean number of procedures (1.8) did not differ significantly between the groups.
Results of Exercise Testing

The mean time from the performance of exercise testing to the follow-up angiogram that documented the absence of restenosis did not differ significantly between the groups (Table 1). The mean maximal ST-segment depression in the patients with positive results on exercise testing, who made up 50% of the total population (ExT Pos group, n=35), was 2.3±0.9 mm. The mean maximal ST-segment depression in the patients with negative results on exercise testing (ExT Neg group, n=35) was 0.3±0.5 mm. The lead that showed the most marked ST-segment depression was a lateral lead (V₄, V₅, V₆) in 59 patients (84%). Ten of the patients in the ExT Pos group developed atypical chest pain during exercise. The symptoms during the exercise test were unlike the chest pain experienced during the initial admission for unstable angina; no exercise test was terminated because of atypical chest pain. There were no significant differences between the groups with respect to Exercise duration, rate-pressure product at rest, or rate-pressure product at peak exercise (Table 2).

![Diagram of regional wall motion assessment.](image)

**Fig 1.** Evaluation of segmental wall motion using a 20-segment model. Values expressed as mean±SD were calculated from a group of 30 control patients. Left ventricular cineangiogram was performed in the right anterior oblique projection (30°); end-diastolic and end-systolic contours were manually outlined and were then digitized into a 386 PC computer. Segmental wall motion was measured by the radial method. Five regional wall motion (RWM) indexes were studied to analyze the anterior wall (RWM, through RWM₅) and the apex (RWM₅₁ and RWM₅₂). EF indicates ejection fraction.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Clinical and Angiographic Data</th>
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<tr>
<td><strong>Total Population</strong></td>
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<tr>
<td>(n=70)</td>
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<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Women, n (%)</td>
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<tr>
<td>Smokers, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes, n (%)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
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<tr>
<td>Family history of cardiovascular disease, n (%)</td>
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<tr>
<td>Mean time, d</td>
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<tr>
<td>From onset of symptoms to the angioplasty</td>
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<tr>
<td>From angioplasty to final angiography</td>
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<tr>
<td>From exercise test to final angiography</td>
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<tr>
<td>Stenosis Location, n</td>
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<tr>
<td>Proximal LAD</td>
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<tr>
<td>Middle LAD</td>
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ExT Neg group indicates patients without significant ST-segment depression on exercise; ExT Pos group, patients with significant ST-segment depression on exercise; diabetes, fasting blood sugar >6.8 mmol/L; hypercholesterolemia, cholesterol >240 mg/dL; proximal LAD, lesion in left anterior descending coronary artery before the first large septal perforator; and middle LAD, lesion in left anterior descending coronary artery after first large septal and before first diagonal. Values are given as mean±SD when appropriate; values in parentheses are percentages of the total numbers in each group.
Quantitative Coronary Angiographic Analysis

The proportion of lesions that were located in the proximal or mid left anterior descending artery did not differ significantly between the groups. Mean values for percent stenosis severity before and immediately after angioplasty and at follow-up angiography (73±11%, 34±8%, and 34±11%, respectively) in the ExT Pos group did not differ significantly from the values in the ExT Neg group (76±12%, 31±11%, and 38±10%, respectively) (Table 3). The mean minimal lumen diameter at follow-up angiography in the ExT Pos group (1.70±0.40 mm) was not significantly different from the value in the ExT Neg group (1.90±0.50 mm) (Table 3).

Quantitative Analysis of Global and Regional Ventricular Function

The mean EF in the total study population 6 months after the final, ultimately successful, angioplasty (70±7%) was significantly (P<.001) higher than the value before angioplasty (65±8%) (Table 4). At follow-up angiography, 68 patients (97%) had EFs within the normal range for our laboratory. Regional anterior wall motion indexes followed a similar pattern. RWM<sub>L</sub> through RWM<sub>R</sub> increased by a mean of 29% between angioplasty and follow-up. Of the hemodynamic variables studied, only LVSP and LVESVI were significantly different at follow-up angiography compared with preangioplasty values (Table 4). LVESP at follow-up angiography (140±23 mm Hg) was significantly (P<.001) higher than that (131±22 mm Hg) before angioplasty. The LVESVI at follow-up angiography (24±10 mL/m²) was significantly (P<.001) less than that (28±10 mL/m²) before angioplasty.

Comparison Between Groups With and Without Exercise-Induced ST-Segment Depression

Before angioplasty, the mean EF (63±8%) in the ExT Pos group (n=35) was significantly (P<.05) less than that (68±9%) in the ExT Neg group (n=35). However, mean EF at final angiographic evaluation in the ExT Pos group (69±8%) was not significantly different than that for the ExT Neg group (71±6%). Thus, although global EF had been significantly lower in the ExT Pos group than in the ExT Neg group before angioplasty, there was no difference between groups at the final angiographic evaluation after successful angioplasty (Table 5). This reflects the fact that although the mean EF in the ExT Pos group increased significantly (P<.01) from 63±8% before angioplasty to 69±8% at follow-up angiography, the mean EF in the ExT Neg group did not change significantly during this time.

Segmental analysis of left ventricular function demonstrated that the ExT Pos group had a significant impairment of anterior wall motion before angioplasty compared with the ExT Neg group. The extent of fractional shortening in the anterior wall segments we

<table>
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<th>TABLE 2. Results of Exercise Testing</th>
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<tr>
<td><strong>Total Population (n=70)</strong></td>
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<tr>
<td>ST depression, mm</td>
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<tr>
<td>Chest pain, n (%)</td>
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<tr>
<td>Rate-pressure product at rest</td>
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<tr>
<td>Time to 1-mm ST depression, min</td>
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<td>Rate-pressure product at 1-mm ST depression</td>
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<td>Total exercise time, min</td>
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<td>Rate-pressure product at peak exercise</td>
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ExT Neg group indicates patients without significant ST-segment depression on exercise; ExT Pos group, patients with significant ST-segment depression on exercise; and rate-pressure product, heart rate (beats per minute)×systolic blood pressure (mm Hg). Values are given as mean±SD where appropriate.

*P<.001 ExT Pos group vs ExT Neg group.

<table>
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<tr>
<th>TABLE 3. Quantitative Angiographic Data</th>
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<tr>
<td><strong>ExT Pos group (n=35)</strong></td>
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<tr>
<td><strong>Angioplasty</strong></td>
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<tr>
<td>Stenosis before angioplasty, %</td>
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<td>Stenosis after angioplasty, %</td>
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<tr>
<td><strong>Follow-up angiography</strong></td>
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<tr>
<td>Stenosis severity, %</td>
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<td>Minimum luminal diameter, mm</td>
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ExT Pos group indicates patients with significant ST-segment depression on exercise; ExT Neg group, patients without significant ST-segment depression on exercise. Values are given as mean±SD.
studied is detailed in Fig 2 and Table 5. The percent fractional shortening on the ventriculogram obtained before angioplasty was significantly \(P<.05\) lower in four of the five segments studied in the ExT Pos group compared with the ExT Neg group. In the ExT Neg group, percent fractional shortening was within the normal range in all anterior wall segments studied on the ventriculogram obtained before angioplasty; at follow-up angiography, all the measurements were again within the normal range and had not changed significantly compared with before angioplasty. In the ExT Pos group, there was a significant improvement in percent fractional shortening in all anterior wall segments between the initial (preangioplasty) and follow-up (after successful angioplasty without restenosis) ventriculograms. The extent of this improvement ranged from 31% in RWM\(s\), \(P<.01\) to 53% in RWM\(_4\), \(P<.01\), and all values were within the normal range. The relation of anterior wall function before angioplasty to the occurrence of a positive or negative exercise test at control angiography was assessed by dividing the patients into two groups based on the quantitative assessment of anterior wall function. Anterior wall contractility before angioplasty was classified as normal (n=36) if the percent fractional shortening was within the normal range for all five anterior wall segments studied. Anterior wall contractility before angioplasty was classified as depressed (n=34) if the percent fractional shortening was less than normal for two or more of the segments studied. The presence of depressed contractility before angioplasty was significantly \(P<.01\) associated with the occurrence of significant ST-segment depression on exercise testing at control angiography (Table 6).

The ExT Pos group also had a significantly \(P<.05\) greater end-systolic volume (LVESVI, 30±11 mL/m\(^2\)) before angioplasty than the ExT Neg group (25±9 mL/m\(^2\)). This parameter did not differ significantly between groups at follow-up angiography. This was due to the significant \(P<.05\) decrease in LVESVI from 30±11 to 25±12 mL/m\(^2\) that occurred in the ExT Pos group between angioplasty and follow-up; the LVESVI in the ExT Neg group did not change significantly during this time. The other hemodynamic parameters studied (Table 5) did not differ significantly between groups either before angioplasty or at follow-up angiography.

**Discussion**

The major and original finding of this study is that exercise-induced ST-segment depression on exercise testing in patients without restenosis after successful one-vessel coronary angioplasty is strongly associated with the presence of localized hypokinesis before angioplasty.
The presence of exercise-induced ST-segment depression in some but not in a few patients without restenosis might be related to a difference in the absolute diameter of the angiographically normal nondilated vessel between groups. Such a difference could result from the presence of occult atherosclerosis in angiographically smooth vessels; indeed, recent intravascular ultrasound studies demonstrated that vessel segments that appear normal on angiography in patients with focal epicardial stenosis have ultrasonic characteristics compatible with the presence of diffuse atherosclerosis. The presence or absence of ST-segment depression on exercise might also be related to differences in the absolute minimal residual lumen diameter at the dilated site. The results of the present study exclude these hypotheses in our patients because mean percent residual stenosis at the dilated site in the ExT Pos group was significantly greater than in the ExT Neg group.

**Fig. 2.** PLOTS OF REGIONAL WALL MOTION (RWM) INDEXES BEFORE (B) AND AT FINAL ANGIOGRAPHIC CONTROL (C) IN THE TWO GROUPS. EXTEST POS GROUP INDICATES GROUP OF PATIENTS WHO HAD SIGNIFICANT ST-SEGMENT DEPRESSION DURING EXERCISE TESTING; EXTEST NEG GROUP, GROUP OF PATIENTS WHO HAD NEGATIVE EXERCISE TEST RESULTS. **P<.01, ***P<.001, BEFORE VS 6 MONTHS AFTER THE LAST ANGIOPLASTY. †P<.05, ††P<.01, EXTEST NEG GROUP VS EXTEST POS GROUP. THERE WAS A SIGNIFICANT INCREASE IN CONTRACTILITY IN ALL SEGMENTS STUDIED IN THE EXTEST POS GROUP BUT NO SIGNIFICANT CHANGE IN THE EXTEST NEG GROUP.
site and mean minimal lumen diameter at the dilated site did not differ between groups with positive or negative results on exercise testing.

A recent study has suggested that ST-segment depression occurring 1 week after angioplasty in the absence of restenosis may reflect functional alterations in small coronary vessels. Such alterations might be present before angioplasty or could be related to the procedure itself. The natural history of ST-segment depression occurring early after angioplasty has not been well defined. It has been suggested that such ST-segment depression is a predictor of subsequent restenosis. It is thus unclear whether the ST-segment depression in our patients 6 months after successful angioplasty has the same pathophysiological basis as that occurring after the procedure. A sequential study of coronary flow reserve immediately after and at 6 months after coronary angioplasty demonstrated an impairment of coronary flow reserve just after the procedure that is related to an increase in resting blood flow that had resolved at 6 months. However, the relation between coronary flow reserve at 6 months and the occurrence of exercise-induced ST-segment depression in the absence of restenosis has not been specifically examined. The results of the present study are compatible with the hypothesis that alterations in the functional characteristics of small coronary vessels present before angioplasty or related to the performance of angioplasty may persist on a long-term basis. Experimental studies show that anatomic or functional alterations in microvascular function are present in hibernating or stunned myocardium. Such alterations in microvascular function probably are also present in the clinical syndrome of unstable angina. Although the anatomic microvascular changes are rapidly reversed when normal basal flow is restored, the functional alterations persist for much longer periods. By limiting coronary flow reserve, such functional alterations could be associated with positive results on exercise testing due to exercise-induced myocardial ischemia despite the relief of epicardial mechanical obstruction by angioplasty.

An alternative explanation for exercise-induced ST-segment depression in this population is that it reflects changes in the electrical properties of myocardial cells or metabolic adaptations related to prior episodes of unstable angina even when myocardial function at rest has normalized. Further studies are needed to elucidate these hypotheses.

Study Limitations

Because exercise was not performed during coronary angiography, we cannot exclude the possibility that exercise-induced ST-segment depression is related to the occurrence of coronary vasospasm during exercise. This, however, is unlikely as none of the patients had a history suggestive of variant angina; furthermore, exercise-induced coronary spasm is more commonly associated with ST-segment elevation than with ST-segment depression during exercise testing. Second, because the left ventriculogram was obtained at rest, we cannot determine whether the ST-segment depression that we observed during exercise reflects alterations in left ventricular function on exercise.

Conclusions

Our results confirm the findings of several previous studies that demonstrated an improvement in the function of myocardium in the territory supplied by a significant coronary stenosis after successful revascularization. The major and novel finding of this study is that the occurrence of a false-positive exercise response after revascularization by angioplasty is directly related to the presence of preprocedural impaired left ventricular dysfunction. The pathophysiological mechanism of this finding remains to be elucidated.

Acknowledgment

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References


Exercise-induced ST-segment depression in patients without restenosis after coronary angioplasty. Relation to preprocedural impaired left ventricular function.
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