Clinical and Prognostic Usefulness of Supine Bicycle Exercise Echocardiography in the Functional Evaluation of Patients Undergoing Elective Percutaneous Transluminal Coronary Angioplasty

Armando Dagianti, MD, FESC; Salvatore Rosanio, MD, PhD; Maria Penco, MD; Alessandra Dagianti, Jr, MD; Susanna Sciomer, MD; Monica Tocchi, MD; Luciano Agati, MD; Francesco Fedele, MD

the Divisions of I Cardiology and III Cardiology, Department of Cardiovascular and Respiratory Sciences, La Sapienza University, Rome, and the Department of Cardiology (M.P.), University of L'Aquila, Italy.

Correspondence to Salvatore Rosanio, MD, PhD, Via FM Guidi 11, 82100 Benevento, Italy.

Abstract

Background Supine bicycle exercise echocardiography (SBEE) has never been used before and early after percutaneous transluminal coronary angioplasty (PTCA) for assessing the functional outcome of the procedure and predicting late restenosis.

Methods and Results We selected 76 subjects with stable angina, normal wall motion at rest, and exercise-induced wall-motion abnormalities before PTCA. SBEE with peak exercise imaging and
the use of a 16-segment, four-grade score model was performed 54±15 hours after PTCA. No exercise-related adverse events occurred. Patients were grouped according to SBEE results: group 1 (n=35, 46%) with negative exercise ECG and echo; group 2 (n=19, 25%) with a positive exercise ECG but normal echo; and group 3 (n=22, 29%) with a positive exercise echo with either a positive (n=7, 32%) or negative (n=15, 68%) ECG. Exercise performance significantly improved in all groups. In group 3, peak wall-motion score index decreased from 1.27±0.11 before to 1.15±0.06 after PTCA (P<.05), and duration of wall-motion abnormalities went from 81±24 to 47±19 seconds (P<.05). The rate of clinical restenosis (ie, angina recurrence or positive 6-month SBEE in asymptomatic patients, both associated with angiographic restenosis >50%) was 37%. By multiple logistic regression analysis, clinical restenosis was associated with a positive post-PTCA exercise echo (odds ratio [OR] 3.08, 95% confidence interval [CI] 1.66 to 5.72; P=.0004) and with increasing values of pre-PTCA wall-motion score index (OR 2.86, 95% CI 1.92 to 4.27; P=.005) and duration of wall-motion abnormalities (OR 2.12, 95% CI 1.07 to 4.20; P=.04).

Conclusions SBEE is a safe and reliable tool to demonstrate changes in exercise-induced wall-motion abnormalities after PTCA and provides prognostic information in the risk assessment of clinical restenosis.

Key Words: exercise • echocardiography • angioplasty • restenosis

Introduction

The noninvasive functional evaluation of patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA) is of paramount importance for clinical decision making and prognostication. Although exercise ECG is the most common approach for screening elective angioplasty candidates, its low sensitivity in single-vessel disease and inability to provide information about the extent of induced left ventricular dysfunction particularly restrict its usefulness in this clinical setting. Exercise echocardiography has recently achieved increased popularity as a powerful diagnostic and prognostic tool.\(^1\)\(^2\)\(^3\)\(^4\) The ability to detect and locate transient exercise-induced left ventricular regional wall-motion abnormalities, corresponding to the perfusion territories of individual coronary arteries, makes this technique particularly suitable for selecting patients for PTCA and assessing the functional outcome of the procedure. Nevertheless, there is a paucity of published studies on exercise echocardiography before and early after angioplasty,\(^5\)\(^6\) and supine bicycle exercise echocardiography (SBEE) has never been used in this clinical setting. Moreover, we are not aware of any data on the prognostic value of exercise echocardiography performed soon after PTCA for predicting late clinical outcome. The aims of this clinical investigation were (1) to examine the ability of SBEE, with imaging during peak exercise, to detect changes in exercise-induced left ventricular regional wall-motion abnormalities soon after successful PTCA and (2) to evaluate the prognostic usefulness of SBEE
in predicting late clinical restenosis within 6 months of follow-up.

Methods

Study Protocol
Seventy-six consecutive patients with chronic stable angina (symptoms stable for the preceding 6 months) in whom elective PTCA was planned were prospectively enrolled. Entry criteria were as follows: (1) normal left ventricular wall motion at rest; (2) exercise-induced wall-motion abnormalities on SBEE performed within 48 hours before angioplasty while patients were receiving medical therapy; (3) significant stenosis in at least one major epicardial coronary segment without occluded coronary lesions; and (4) angiographically successful single PTCA of the vessel supplying the myocardial territory where ischemia was detected by SBEE. After PTCA, patients were submitted to SBEE as soon as possible after discontinuation of medical therapy for at least 24 hours except for the administration of 100 to 300 mg/d of oral aspirin. The study group was then scheduled for clinical follow-up; the end point was clinical restenosis within 6 months of angioplasty, defined either as recurrent anginal symptoms requiring repeated angiography associated with restenosis or as positive SBEE at 6 months in asymptomatic patients with subsequent angiographic evidence of restenosis. Patients with exercise echocardiographic imaging technically unsuitable for interpreting and scoring regional wall motion, baseline ECG alterations (digitalis, left ventricular hypertrophy, or left bundle-branch block) that could interfere with the diagnosis of myocardial ischemia, previous bypass surgery or angioplasty, previous myocardial infarction, congenital or acquired valvular heart disease, cardiomyopathy, or significant left main disease were excluded. The study protocol was approved by La Sapienza University Ethical Committee on Human Research, and informed consent was obtained in writing from all subjects.

SBEE
The exercise test was performed with supine bicycle ergometry on a tilting exercise table, with the table tilted to 30° of the left lateral decubitus position. Exercise was started with a work load of 25 W that was increased by 25 W every 2 minutes. When testing was not interrupted by symptoms (angina, severe fatigue, or dyspnea) or the onset of echocardiographic or ECG signs of myocardial ischemia, the value of 85% of maximum age-predicted heart rate was always reached. Two-dimensional echocardiographic examination was performed with the use of commercially available wide-angle, phased-array imaging systems (Hewlett-Packard 1000 and 1500 and Vingmed Sonotron CFM 800) immediately before and throughout the entire test and recovery period, with standard parasternal and apical views acquired in the supine position as previously reported. Echocardiographic studies were digitized on-line at rest and at peak exercise. For a comparison of images at rest and during exercise and an accurate wall-motion analysis, a continuous-loop, quad-screen–format display of the echocardiographic views was used. The left ventricle was divided into 16 segments with use of a standard model, and wall motion was quantitatively assessed by the evaluation of systolic thickening as normal (>5 mm), hypokinetic...
(2- to 5-mm excursion), akinetic (absent thickening), or dyskinetic (systolic wall thinning and outward motion). The wall motion of each individual segment was graded by attributing a score of 1 if normal, 2 if hypokinetic, 3 if akinetic, and 4 if dyskinetic. The location of segmental wall-motion abnormalities was correlated with coronary arterial distribution by a previously described methodology in which the apical lateral and apical inferior segments were considered to be areas of overlap. The apical lateral segment was considered to be a part of the left anterior descending artery territory in association with additional septal or anterior asynergies. The same segment was considered to be a part of the left circumflex artery distribution in association with posterior or posterolateral wall-motion abnormalities. The apical inferior segment was related to the right coronary artery system if there were additional inferior wall-motion abnormalities and to the left anterior descending artery region in the presence of anterior or anteroseptal asynergies. A one-grade increase in score in ≥1 segments from rest to peak exercise was considered a positive test. Using this scoring system, we calculated an index of global left ventricular wall motion (wall-motion score index) as the sum of scores in visualized segments divided by the number of segments visualized at rest and peak exercise for both studies before and after PTCA. Backup videotape image analysis was used to estimate the duration of wall-motion abnormalities, defined as the time interval between the frame showing abnormal thickening of at least one segment and the frame showing completely restored normal wall motion. Echocardiographic recordings were coded and interpreted at random by two of the investigators, who were blinded to clinical data, with an interobserver agreement on 92% of the examined segments. One observer reviewed a random sample of 80 studies twice, with an intraobserver agreement on 98% of the examined segments. Measurements of the duration of wall-motion abnormalities were repeated by two observers and by the same observer on different days without knowledge of earlier results. No systematic differences were noted between three paired measurements (mean difference, 0.59±4.07; t=.74; P=.4). Regression of the absolute difference between the duration of wall-motion abnormality measurements on its mean measurement gave F=.15, P=.7. Continuous 12-lead ECG monitoring was used at rest, during exercise, and up to 10 minutes after exercise, and a 12-lead ECG, cuff arterial blood pressure, and heart rate were recorded at baseline, the end of each exercise stage, peak exercise, and 3 and 6 minutes into the recovery period. A positive exercise-ECG response was defined as the development of >0.1 mV horizontal or downsloping ST-segment depression or elevation at 0.08 seconds after the J-point in a lead with a normal baseline ST segment.

Quantitative Coronary Angiography and PTCA Procedure
Left-sided cardiac catheterization and coronary angiography were performed in a standard manner. Multiple views of each coronary artery were obtained, including craniocaudal views. After administration of intracoronary nitroglycerin to obtain maximal vasodilation, two near-orthogonal views were digitized that had the least vessel overlap. Using the most severe stenosis projection, we measured reference coronary artery dimensions proximal to the stenosis and minimal lumen diameter with the use of a commercially available quantitative angiographic software program (MIP D Kontron). The percent diameter stenosis was calculated according to the formula \[
\frac{(\text{Reference Diameter-Minimal Diameter})}{\text{Reference Diameter}}\times 100.
\] Significant
stenosis was defined as ≥50% luminal-diameter reduction of any of the major epicardial vessels or their primary branches. Lesion morphology was classified as complex when irregular borders, eccentricity, calcifications, or intraluminal filling defects suggestive of ulcer or thrombus were present. PTCA was performed by a standard technique using the femoral approach and consisted of dilation of a single significant stenosis selected by the catheterizing physician as the ischemia-inducing lesion on the basis of the available SBEE results. At the beginning of the procedure, patients received 10 000 IU of heparin IV as bolus and 0.2 mg of intracoronary nitroglycerin. At the completion of the procedure, a continuous infusion of 1000 IU of heparin IV was started and continued at a dosage sufficient to maintain activated partial thromboplastin time between two and three times the basal values. Balloon dimension was chosen according to the vessel size to optimize the balloon/artery ratio. Note was taken of the number of balloon inflations, maximal inflation time, and maximal inflation pressure. Pressure gradients across the stenosis were measured before and after inflation of the balloon at the stenotic site. After completion of balloon dilation, repeated arteriograms were recorded in the same angiographic views of the pre-PTCA angiography. The angiographic success of PTCA was assessed by a quantitative estimate of residual coronary stenosis <50% of luminal diameter and by the gradation of anterograde flow as a TIMI grade 3 perfusion without angiographic evidence of any large intimal dissection or thrombus at the lesion site, in the absence of myocardial infarction, death, or need for repeat PTCA or bypass surgery during hospitalization.

Follow-up
Follow-up information was obtained from all patients by means of outpatient visits at time intervals of 1, 3, and 6 months, and their clinical condition, drug compliance, and the presence or absence of recurrent anginal symptoms were assessed by means of standardized questionnaires. All data were recorded on standardized forms and entered into a computerized database. At the 6-month visit, all patients who had no prior anginal symptoms underwent SBEE. Patients with angina recurrence and those asymptomatic but with a positive SBEE at 6 months underwent repeat coronary angiography to assess the occurrence of angiographic restenosis (ie, presence of >50% stenosis at the site of the previous PTCA). When angiography showed a progression of coronary artery disease in remote vessels or stenoses distal to the site of previous balloon dilation, patients were not considered to have clinical restenosis and therefore were recorded as negative in follow-up statistical analysis.

Statistics
Continuous measures are expressed as mean±SD or as median and relative ranges; dichotomous variables are presented as percentages. Comparisons of binary variables were performed using the Yates' corrected $\chi^2$ statistic or, when appropriate, Fisher's exact test. Continuous variables were compared by one-way ANOVA. Statistical significance (two-tailed) was inferred at $P<.05$. Sensitivity, specificity, and predictive accuracy values were calculated in the standard manner. Logistic regression analysis based on the maximum-likelihood method was used to evaluate the association between clinical, angiographic, echocardiographic, and exercise testing variables and the occurrence of clinical restenosis. Clinical restenosis was regarded as the dependent variable, and all other variables were regarded as independent variables, appropriately classified as
quantitative or categorical. To select covariates independently associated with clinical restenosis, significant univariate predictors were reassessed by a forward stepwise multivariate analysis with values for inclusion and elimination set at \( P = .05 \) and \( P = .10 \) respectively. The likelihood-ratio \( \chi^2 \) value was used to assess multivariate model significance. To estimate the strength of the association between each multivariate predictor and recurrence of clinical restenosis, odds ratios (ORs) and their 95% CIs were computed. The instantaneous ORs for dichotomous variables were calculated from the exponential of the estimated regression coefficient \( \beta \) of the variable, with all other variables in the model remaining constant. The instantaneous OR for a continuous variable for an increase in \( n \) units of that variable is \( \exp(\beta)^n \).

## Results

### Baseline Characteristics
Clinical and angiographic features of the 76 study patients were as follows: the group study consisted of 18 women (24%) and 58 men (76%) with a mean age of 53±8 years (range, 31 to 68 years); 18 (24%) had a history of essential hypertension, 12 (16%) had type II diabetes, 23 (30%) had blood cholesterol >240 mg/dL, and 21 (28%) had a history of cigarette smoking. Fifty-nine patients (78%) were taking calcium channel blockers, 13 (17%) were taking \( \beta \)-blockers, 57 (75%) were taking oral nitrates, and all patients were taking oral aspirin at the time of PTCA. Single-vessel disease was present in the majority of patients (\( n = 56, 74\% \)). Exercise ECG before PTCA was positive in 51 (67%) of 76 patients. Of the 51 patients with a positive exercise ECG, 23 (45%) had ischemic ECG changes in the leads related to the left anterior descending artery, 11 (22%) in the leads related to the circumflex artery, and 17 (33%) in those related to the right coronary artery. The PTCA was performed on the left anterior descending artery in 39 patients (51%), the left circumflex artery in 19 (25%), and the right coronary artery in 18 (24%). Lesion morphology was complex in 25 (33%) of the dilated stenoses. The percent coronary stenosis decreased from 78±5% before to 23±4% after PTCA (\( P < .001 \)).

### Exercise Test Results Soon After PTCA
Exercise testing was performed at a mean time of 54±15 hours (range, 36 to 90 hours) after the procedure. All exercise echocardiograms were technically suitable for interpreting and scoring segmental wall motion. No patient was limited by leg pain at the catheter-insertion site or showed any worsening of femoral-area hematomas or developed femoral artery pseudoaneurysm. No patient complained of typical anginal symptoms during exercise testing. Three patients had nonsustained ventricular arrhythmia associated with ischemic ECG changes during exercise, thus not altering test results. On the basis of the results of the post-PTCA exercise test, patients were classified into three groups: group 1 (\( n = 35, 46\% \)) with a negative exercise ECG and echo; group 2 (\( n = 19, 25\% \)) with a positive exercise ECG but normal echo; and group 3 (\( n = 22, 29\% \)) with a positive exercise echo with either a positive (\( n = 7 \) [32%] of 22) or negative ECG (\( n = 15 \) [68%] of 22). In group 3, the site of post-PTCA exercise-induced asynergies was consistent with the site of the dilated vessel, and none of the patients with multivessel disease (\( n = 6 \) [27%] of 22) showed
asynergies in segments supplied by vessels other than the one on which PTCA had been performed. Comparison of physiological variables before and after PTCA provided evidence that all three groups achieved a significant improvement in exercise performance (Table 1). The increase in the rate-pressure product was statistically significant in groups 1 and 2, whereas in group 3 it showed a trend toward statistical significance \((P=.06)\). However, in group 3, exercise capacity and exercise duration after PTCA were both significantly lower than in groups 1 and 2.

In group 3, the peak wall-motion score index was significantly lower after PTCA than before the procedure \((1.15\pm0.06 \text{ versus } 1.27\pm0.11; P<.05)\), as was the duration of wall-motion abnormalities \((47\pm19 \text{ versus } 81\pm24 \text{ seconds}; P<.05)\) (Table 1). On SBEE before PTCA, no differences were found among the three groups in relation to mean rate-pressure product, maximal heart rate, or exercise duration and capacity. However, the mean peak wall-motion score index on pre-PTCA SBEE was significantly greater for group 3 than for group 1 \((1.27\pm0.11 \text{ versus } 1.22\pm0.07; P<.05)\) or group 2 \((1.27\pm0.11 \text{ versus } 1.20\pm0.09; P<.05)\). Furthermore, the mean duration of wall-motion abnormalities in group 3 was significantly higher than in group 1 \((81\pm24 \text{ versus } 71\pm16 \text{ seconds}; P<.05)\) and slightly but not significantly higher than in group 2 \((81\pm24 \text{ versus } 76\pm22 \text{ seconds}; P=\text{NS})\). Comparison among the three groups was also performed in relation to the clinical characteristics, pre-PTCA and post-PTCA angiographic data, and PTCA procedural variables (Table 2). No significant differences were found with respect to dilated vessel, morphological complexity of stenosis, percent stenosis and minimal lumen diameter before and after PTCA, pressure gradient after PTCA, percent of patients with a residual narrowing between 30% to 50% and <30%, and extent of coronary disease, or to any other of the listed variables.

### Table 1. Results of Supine Bicycle Exercise Echocardiography Before and After Angioplasty in Patients Grouped According to Postangioplasty Exercise-Test Response

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-PTCA SBEE</th>
<th>Post-PTCA SBEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.27±0.11</td>
<td>1.22±0.07</td>
</tr>
<tr>
<td>2</td>
<td>1.27±0.11</td>
<td>1.20±0.09</td>
</tr>
<tr>
<td>3</td>
<td>1.15±0.06</td>
<td>1.27±0.11</td>
</tr>
</tbody>
</table>

### Table 2. Clinical, Angiographic, and Procedural Features in Patients Grouped According to Postangioplasty Exercise-Test Response

Relationships Between SBEE Results Early After PTCA and Clinical Restenosis

Of the 76 patients studied, clinical follow-up was achieved in 100%, and angiographic studies were performed at a mean time interval of 4.4±1.6 months (range, 3 to 6 months) in 47 (62%) of the 76 patients. No cases of death or myocardial infarction were recorded. On the basis of prospectively defined criteria, 28 patients (37%) were classified as having clinical restenosis and 48 (63%) as not having clinical restenosis. In the Figure, the relations between exercise echo and ECG results soon after PTCA and the occurrence of symptomatic or asymptomatic restenosis are illustrated. Repeat angiography was performed because of recurrent chest pain in 32 (42%) of the 76 patients, and restenosis was documented in 18 (56%) of those patients. Of the remaining
14 patients (44%) without restenosis, 4 (29%) developed coronary disease progression in remote vessels and 10 (71%) showed an unaltered angiographic status with respect to that observed after completion of balloon dilation. Of the 18 patients with symptomatic restenosis, 1 belonged to group 1, 1 to group 2, and 16 to group 3, 7 of whom had positive exercise ECG on SBEE soon after PTCA. Of the 44 (58%) of 76 patients who remained asymptomatic, 29 (66%) had negative exercise testing for both echo and ECG at 6 months. The remaining 15 patients (34%) with a positive 6-month exercise echo, 8 (53%) of whom also had a positive exercise ECG, underwent repeat angiography. Restenosis at the site of PTCA was found in 10 (67%) of the 15 patients. In all patients in whom clinically silent restenosis was documented, there was excellent concordance between the distribution of exercise-induced wall-motion abnormalities and the angiographic site of restenosis, whereas the exercise ECG was positive in only 4 patients (40%). Of the remaining 5 patients (33%) with a positive 6-month exercise echo, 4 (80%) of whom had a positive exercise ECG, 3 (60%) developed coronary disease progression in remote vessels and 2 (40%) had stenoses distal to the site of previous PTCA. Of the 10 patients with asymptomatic restenosis, 5 belonged to group 1, 3 to group 2, and 2 to group 3. Therefore, as shown in Table 3, exercise echo shortly after PTCA showed a significantly greater specificity than exercise ECG in predicting late clinical restenosis (92% versus 69%; \( P = .01 \)) and a higher sensitivity, with a trend toward statistical significance (64% versus 39%; \( P = .10 \)), whereas predictive accuracy was significantly higher (82% versus 58%; \( P = .003 \)). Separating out the data on symptomatic or asymptomatic restenosis, exercise echo showed sensitivity and specificity for prediction of symptomatic restenosis that were significantly higher than exercise ECG (89% versus 44%, \( P = .01 \); and 90% versus 69%, \( P = .01 \), respectively), whereas the sensitivity and specificity of exercise echo for asymptomatic restenosis were low and not significantly different from those of exercise ECG (20% and 70% versus 30% and 65%; \( P = NS \)).

![Figure 1. Relationships between supine bicycle exercise echocardiography results soon after coronary angioplasty and the occurrence of clinical restenosis (ie, angina recurrence or positive 6-month exercise echo in asymptomatic patients, both associated with angiographic restenosis >50%). SBEE indicates supine bicycle exercise echocardiography; PTCA, percutaneous transluminal coronary angioplasty; ExEcho, exercise echocardiogram; ExECG, exercise ECG; pos, positive response; neg, negative response; SR, symptomatic restenosis; and AR, asymptomatic restenosis.](https://circ.ahajournals.org/cgi/content/full/95/5/1176?maxtoshow=&HITS=10&hits=10&R...)
Logistic Regression Analysis

Among the clinical, angiographic, procedural, and exercise testing variables examined, which are listed in Table 4, covariates significantly associated with clinical restenosis comprised variables relative to either pre-PTCA SBEE (that is, rate-pressure product, peak wall-motion score index, and duration of wall-motion abnormalities) or to early post-PTCA SBEE (ie, a positive exercise echo, exercise capacity, and rate-pressure product). Stepwise multiple logistic regression analysis was used to identify the most parsimonious group of predictors of clinical restenosis. The final model ($\chi^2 3df, 69.65; P<.0001$) included three echocardiographic variables, as shown in Table 5. The strongest predictor associated with clinical restenosis was the positive response of early post-PTCA exercise echo (OR adjusted for other variables in model, 3.08; 95% CI, 1.66 to 5.72); a significant association was noted also with pre-PTCA wall-motion score index (median, 1.25, range, 1.06 to 1.5; adjusted OR, 2.86; 95% CI, 1.92 to 4.27) and with pre-PTCA duration of wall-motion abnormalities (median, 72 seconds; range, 25 to 115 seconds; adjusted OR, 2.12; 95% CI, 1.07 to 4.20). A probability equation was also derived using the stepwise logistic regression coefficients:

$$P\, (\text{Clinical Restenosis}) = \frac{e^{-22.6+4.4(ExEcho)+14.6(WMSI)+0.16(WMA)}}{1+e^{-22.6+4.4(ExEcho)+14.6(WMSI)+0.16(WMA)}}$$

where $P\, (\text{Clinical Restenosis})$ denotes the probability of clinical restenosis, $-22.6$ is the regression constant, WMSI indicates wall-motion score index, and WMA is wall-motion abnormalities. On the basis of this equation, the risk of clinical restenosis for various combinations of the significant predictors can be estimated in this and similar populations.

**View this table:** Table 4. Covariates Associated With Clinical Restenosis by Univariate Logistic Regression Analysis

**View this table:** Table 5. Multivariate Predictors of Clinical Restenosis by Logistic Regression Analysis

### Discussion

The present study shows that SBEE represents a safe, feasible, and reliable diagnostic technique for objectively documenting the impact of PTCA on functional capacity and exercise-induced regional myocardial contractile dysfunction. Moreover, this study is the first to provide data regarding the prognostic usefulness of exercise echocardiography to stratify patients into high- and low-risk subsets for late clinical restenosis.
**Stress Echocardiography and PTCA**

The current study is the first to perform a functional assessment before and shortly after elective angioplasty by SBEE with all images acquired during peak exercise. This precludes the possibility of a comparison with the only two published studies on exercise echocardiography applied in a similar clinical setting. Labovitz et al. used post–treadmill stress echocardiography and observed improvement of both segmental and global left ventricular function in a small group of patients within 2 weeks of angioplasty. Broderick et al. using treadmill exercise and upright bicycle ergometry, demonstrated that resolution of exercise-induced regional wall-motion abnormalities was complete in 28% and partial in 33% of the patients studied. However, that study was performed at a mean time interval of 28±26 days after angioplasty, and therefore it does not necessarily reveal the immediate myocardial functional benefit achieved with PTCA. Moreover, the patients studied were a heterogeneous group including those with previous myocardial infarction, previous bypass surgery, and a high prevalence (>50%) of wall-motion abnormalities at rest, and thus were quite different from our study population. In the present study, we observed a significant improvement in stress-induced regional left ventricular dysfunction in the distribution of the PTCA vessel, consistent with previous studies by dobutamine and dipyridamole echocardiography performed immediately after PTCA. Furthermore, the time of the study after balloon dilation (within 48 hours) and the frequency of patients with persisting positive studies (from 14% to 36%) according to pharmacological stress tests match our present findings. Although pharmacological stress tests may be easier to perform, exercise testing in the present study also proved safe and feasible as early as 36 hours after PTCA, in keeping with previous reports. The relatively high percentage of positive post-PTCA exercise echocardiograms in the present study may be due to several factors: (1) the selection of patients, all of whom had a positive pre-PTCA exercise echo while receiving medical therapy; (2) the fact that after intervention, all patients underwent maximal SBEE after discontinuation of antianginal therapy, which could have reversed inducible ischemia, as demonstrated previously by repeating positive post-PTCA exercise-ECG tests after sublingual isosorbide dinitrate or intravenous administration of verapamil; and (3) the exercise modality and imaging technique (the supine position has been shown to be accompanied by earlier angina and more pronounced left ventricular filling abnormalities and ischemic ST-segment changes than upright exercise, and it allows the ischemic threshold to occur at a lower heart rate, which is helpful for obtaining peak stress images technically suitable for wall-motion analysis). Furthermore, the continuous echocardiographic monitoring from the beginning of exercise to peak and recovery times has enabled us to demonstrate that regional wall-motion abnormalities immediately after angiographically successful PTCA were of moderate severity and short duration; therefore, it is likely that they may not be detected by imaging after exercise, while ischemia is progressively resolving.

**Possible Pathophysiological Mechanisms**

The mechanism responsible for exercise-induced myocardial ischemia soon after successful PTCA is poorly understood. Whether fixed anatomic obstruction (delayed elastic recoil or local...
thrombosis) sufficient to limit coronary flow during exercise and result in a positive SBEE is already present in the immediate postangioplasty period is not clear from the present study. However, according to a recent angiographic report, the occurrence of delayed elastic recoil and early luminal deterioration seems uncommon after successful and uncomplicated angioplasty.19 Moreover, to prevent mural thrombus formation, our patients were fully anticoagulated and treated with aspirin, which proved effective in reducing early coronary thrombosis after PTCA.20 A plausible explanation for positive early post-PTCA stress echocardiograms is that coronary flow reserve may not have been restored to normal by the balloon dilation due to angiographically unrecognized inadequate lumen expansion, which may itself be a determinant of late restenosis. This interpretation is supported by recent preliminary studies21 22 using intracoronary ultrasound imaging and Doppler methods that demonstrated that after PTCA, flow reserve does not normalize in a substantial minority of patients, whereas stent placement in a post-PTCA vessel with persistent impaired flow reserve results in timely normalization of coronary flow in the vast majority of subjects, probably because of better lumen enlargement, elimination of dissection, and improvement in laminar flow. The finding that higher pre-PTCA wall-motion score and duration of asynergies were independently associated with the occurrence of clinical restenosis is noteworthy and has not been documented previously. The larger amount of pre-PTCA myocardial dysfunction in the patients with persistent inducible wall-motion abnormalities after PTCA was not explained by a different angiographic status (morphological complexity and severity of stenoses, extent of coronary disease, or dilated vessel) or a dissimilar myocardial oxygen demand (ischemic threshold or exercise duration) with respect to patients with full recovery of asynergies after intervention. The lack of a clear correlation between angiographic variables and the magnitude of regional contractile dysfunction detected by exercise echocardiography is in keeping with previous observations by Hecht et al23 24 and might reflect the limitations of angiography in appraising the extent and distribution of underlying atherosclerosis and in predicting its functional significance.25 26 27 It is thus possible that the presence of a strongly positive exercise echo before or after PTCA identifies patients with more severe coronary disease, which is underestimated by angiographic luminal measurements. To clarify our clinical observations, the results of exercise echocardiography should be evaluated in comparison with a direct measure of the physiological state of coronary flow reserve and using intracoronary ultrasound or a suitable alternative for full interrogation of the diseased vessel wall.

Role of Exercise Echocardiography in Predicting Clinical Restenosis

Restenosis within the first 6 months after coronary intervention continues to be one of the most vexing problems in cardiology, placing 35% to 50% of patients treated at risk for angiographic renarrowing and at least 25% to 35% of patients at risk for clinical recurrence.28 29 Any approach that would identify a subset of PTCA patients at increased risk would have important clinical value. The prognostic usefulness of functional testing immediately after PTCA for predicting late restenosis has been investigated previously,11 12 16 but no study on exercise echocardiography has been reported to date. The current study demonstrates that the detection of persistent exercise-induced regional wall-motion abnormalities soon after a successful PTCA represents a specific indicator for identifying patients at risk for late clinical restenosis. The sensitivity of an
early post-PTCA exercise echo appears excellent for prediction of patients who will have symptomatic restenosis but limited for patients with clinically silent restenosis. As suggested by a recent observation\textsuperscript{30} that the magnitude of myocardial dysfunction assessed by exercise echocardiography is greater in painful than in painless myocardial ischemia, it is possible that symptomatic restenosis may occur in patients with larger areas of contractile dysfunction or more severe ischemia, which may be easier to detect by echocardiographic imaging. Our results compare well with those obtained by dipyridamole echocardiography, demonstrating that the presence of stress-induced asynergies soon after successful angioplasty identified a group of patients at high risk for later recurrence of symptoms due to coronary restenosis.\textsuperscript{11, 12} In the present study, exercise ECG offered limited prognostic information, in keeping with previous data reported by Deligonul et al\textsuperscript{31} showing that standard exercise ECG performed an average of 9 days after successful PTCA is not predictive of cardiac events in patients with single-vessel disease. Similarly, Balady et al\textsuperscript{14} found that exercise ECG 1 to 3 days after PTCA did not yield discriminatory information regarding the likelihood of future restenosis or cardiac events. Finally, an intriguing finding from the present study was the significant association between clinical restenosis and the amount and duration of exercise-induced regional contractile dysfunction before balloon angioplasty. Although our model cannot be used predictively in a clinical setting until prospectively tested on an independent sample of patients, these results are clinically relevant because they suggest that the quantitation of regional ventricular dysfunction by exercise echocardiography may be useful to identify individuals at risk to develop restenosis before PTCA is performed.

**Study Limitations**

Some of the difficulties concerning the clinical applicability of the data obtained in this clinical investigation should be mentioned. Of course, SBEE requires an acceptable acoustic window in the resting condition and considerable expertise for the acquisition of the exercise images and interpretation of the test. In addition, exercise echocardiography cannot be used effectively to assess the results of PTCA in those patients who have a negative test before the procedure. The main limitation in the present study is that only patients with clinical restenosis were identified. None of the 29 asymptomatic patients who had negative exercise testing for both echo and ECG at 6 months (38% of the study population) underwent catheterization, and obviously some patients in this group had restenosis. To be consistent with recent recommendations for clinical trials,\textsuperscript{32} and also because borderline luminal-diameter narrowing (40% to 70%) by quantitative coronary angiography correlates poorly with both clinical symptoms and prognosis,\textsuperscript{33} we prospectively chose a clinically relevant definition of recurrence that required recurrent symptoms or inducible ischemia with angiographically demonstrated restenosis. Maximal SBEE, which in our laboratory has very high sensitivity and specificity for identifying significant coronary stenoses,\textsuperscript{2, 7} was used to assess clinical recurrence in asymptomatic patients. A negative maximal SBEE probably identified patients with very little, if any, angiographic restenosis, because the probability of restenosis in asymptomatic patients with negative exercise ECG is \(\approx 5\% .\textsuperscript{34}\) Therefore, follow-up cardiac catheterization in our asymptomatic patients with negative exercise testing for both echo and ECG would have been neither ethically justified nor cost-
effective and would have provided few additional data on the incidence of restenosis. Some doubts about the safety of earlier testing were cast by previous case reports\textsuperscript{35, 36} documenting the onset of acute coronary occlusion or myocardial infarction within minutes of exercise testing after successful PTCA. Nevertheless, the present study proves that symptom-limited exercise testing soon after PTCA is feasible and safe in appropriately screened patients, in accordance with other observations\textsuperscript{11, 14, 15, 16} However, our data do not apply to all patients undergoing PTCA because they were derived from a selected subset with stable angina and normal resting global and regional myocardial function. Finally, it is not likely that a patient would be removed from all antianginal medications after angioplasty, and this is a limitation of the study with regard to its applicability to a clinical situation.

**Clinical Implications**

In patients with chronic stable angina who are being evaluated for PTCA, objective evidence of myocardial ischemia while they are receiving medical therapy during laboratory testing is required before the patients are subjected to the potential risks of PTCA, restenosis, or both\textsuperscript{37} In the current environment of cost control, the demonstration of ischemia within the territory of a vessel that could potentially be treated with angioplasty may be used to justify such an intervention. Exercise echocardiography offers more specific data on the site and extent of ischemia than does exercise ECG alone, at a lower cost than nuclear techniques. Moreover, the measurement of regional ventricular dysfunction with imaging during exercise provides incremental information, because more severe and longer-lasting preprocedural asynergies appear to develop in patients in whom the PTCA fails to normalize exercise wall motion. These data imply that decisions about larger angioplasty balloon dilation or stent placement might be made in advance for patients with larger areas of myocardium in jeopardy. Although most patients with restenosis present with angina and not a major cardiac event, the possibility that individuals at increased risk might be identified by an early postangioplasty SBEE may help to establish comprehensive risk-factor–modification programs and implement early nonpharmacological and pharmacological measures aimed at preventing restenosis, as recently outlined by the American Heart Association\textsuperscript{38} Although these considerations would justify a more extensive use of SBEE in this clinical setting, we are aware that additional data on larger groups of patients are needed. With such data, it may be possible not only to confirm the preliminary findings of the present study, but also to better define the cost/benefit ratio for performance of SBEE both before and after interventional procedures.

**Acknowledgments**

The authors thank Renato Coppi, PhD, Department of Statistics, La Sapienza University, Rome, Italy, and Jorge Blanco, PhD, Instituto de Estadistica, Universidad de la Republica, Montevideo, Uruguay, for their valuable expertise.

**Footnotes**
References


33. Gordon PC, Friedrich SP, Piana RN, Kugelmass AD, Leidig GA, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS. Is 40% to 70% diameter narrowing at the site of previous stenting or directional coronary atherectomy clinically significant? *Am J Cardiol.*. 1994;74:26-32.[Medline] [Order article via Infotrieve]


