Quantitative Angiographic Measurements of Isolated Left Anterior Descending Coronary Artery Stenosis

Correlation With Exercise Echocardiography and Technetium-99m 2-Methoxy Isobutyl Isonitrile Single-Photon Emission Computed Tomography

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Objectives. This study sought to assess the value of quantitative coronary arteriography in predicting an ischemic response at exercise echocardiography and technetium-99m 2-methoxy isobutyl isonitrile (mibi) single-photon emission computed tomography (SPECT) in patients with single-vessel disease of the left anterior descending coronary artery.

Background. The relation between severity of coronary stenosis and ischemic response to exercise echocardiography and perfusion scintigraphy in patients with single-vessel left anterior descending coronary artery disease is not well established.

Methods. Thirty-one patients without a previous myocardial infarction who had isolated stenosis of varying degrees in the proximal or midportion of the left anterior descending coronary artery were studied. Quantitative arteriographic analysis was used for measurements of percent diameter stenosis and minimal lumen diameter. Exercise-induced wall motion abnormalities by echocardiography and transient perfusion defects by mibi SPECT were considered a positive response. The analysis of sensitivity/specificity and receiver operating characteristic curves was applied to establish the diagnostic power of quantitative coronary arteriography to predict an ischemic response to exercise echocardiography and mibi SPECT.

Results. The “best” angiographic cutoff values for predicting a positive exercise echocardiographic and scintigraphic response were similar (diameter stenosis 52%, minimal lumen diameter 1.12 mm for echocardiography; diameter stenosis 49%, minimal lumen diameter 1.20 mm for SPECT). However, the sensitivity/specificity at the cross point was slightly higher (even if not statistically significant) for echocardiography than for SPECT, both for diameter stenosis (81% vs. 67%) and minimal lumen diameter (81% vs. 74%), suggesting that quantitative coronary arteriographic measurements are more closely related to echocardiographic than scintigraphic exercise test results.

Conclusions. The functional significance of a proximal/mid-left anterior descending coronary artery stenosis measured by quantitative coronary arteriography is slightly better related to echocardiographic than scintigraphic markers of exercise-induced myocardial ischemia.

Anatomic information derived from arteriography is not always predictive of the physiologic significance of a coronary stenosis (1). Several noninvasive techniques have been proposed to assess the functional significance of a coronary stenosis detected by contrast arteriography. Exercise testing in conjunction with echocardiography (2–4) or perfusion scintigraphy (5,6) has been used extensively for the evaluation of patients with suspected or known coronary artery disease, and data available on the comparative value of the two methods in the same population demonstrate that they have similar diagnostic accuracy (7–12). However, in these previous studies, coronary arteriography was not quantitatively evaluated, and the confounding effects of previous myocardial infarction and abnormal wall motion at rest were not always avoided. Accordingly, we determined to investigate which quantitative angiographic variable best correlates with exercise-induced wall motion abnormalities and transient perfusion defects. To this end, a selected patient group with proximal or mid-left anterior descending coronary artery stenosis and no previous myocardial infarction was studied, and receiver operating characteristic curve analysis was used as an objective method for determining the power of quantitative angiographic variables for the prediction of an abnormal exercise echocardiographic and single-photon emission computed tomographic (SPECT) response.

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Methods
We selected 31 consecutive patients (23 men, 8 women; mean [±SD] age 57 ± 11 years, range 32 to 78) referred for evaluation of chest pain or enrolled in follow-up studies after percutaneous coronary angioplasty who fulfilled the following inclusion criteria: 1) proximal or mid–left anterior descending coronary artery stenosis at arteriography judged from mild to severe by visual assessment; 2) no history of previous myocardial infarction; 3) simultaneous exercise echocardiography and technetium-99m 2-methoxy isobutyl isonitrile (mibi) SPECT performed within 2 weeks of coronary arteriography; 4) normal wall motion and perfusion at rest. Patients with unstable angina were excluded.

Exercise testing procedure. Symptom-limited upright bicycle ergometry was performed with stepwise increments of 20 W/min. The electrocardiogram (ECG) was continuously monitored (leads II, V2, V5), and a 12-lead ECG was recorded at rest and each minute throughout the test. Cuff blood pressure was measured at rest and every 2 min. The ECG was analyzed by a computer-assisted system (Cardiovit CSG/12, Schiller), and a horizontal or downsloping ST segment depression ≥1 mm occurring 80 ms after the J point was considered ischemic.

Exercise echocardiography. Two-dimensional echocardiograms were acquired with a wide-angle phased-array system equipped with either a 2.5- or 3.5-MHz transducer. Rest images were acquired in the standard views (parasternal long- and short-axis, apical four- and two-chamber), with the patients in the left lateral decubitus position. Postexercise images were obtained immediately after the termination of exercise testing, with the patients lying in the same rest position. The first stress images were always acquired within 1 min of the termination of exercise.

Both rest and stress images were recorded on videotape, digitized on-line and stored for subsequent analysis.

Analysis of exercise echocardiography. Rest and exercise digitized two-dimensional images were reviewed on a side-by-side cine-loop display and videotape. Images were interpreted by two experienced investigators who were unaware of the patient's clinical data and exercise ECG and angiographic results. Agreement between the two observers was required for the classification of the wall motion abnormalities. In case of disagreement, the opinion of a third investigator was binding. For purpose of analysis, left ventricular wall motion was evaluated on a 16-segment model, and each segment was scored using a four-point scale: 1 = normal wall motion and thickening; 2 = hypokinesia; 3 = akinesia (absence of systolic wall motion and thickening); and 4 = dyskinesia (systolic outward wall motion with thinning). An ischemic response was defined as an exercise-induced wall motion abnormality. The low level of interobserver and intraobserver variability obtained in our laboratory for the interpretation of exercise echocardiography has been reported elsewhere (8). The location of wall motion abnormalities was correlated with coronary arterial distribution by using the methodology described by Segar et al. (13).

Exercise mibi SPECT. About 1 min before the termination of the exercise stress test, 370 MBq of technetium-99m mibi was injected in an antecubital vein through a previously inserted cannula. Stress SPECT images were acquired 1 h after injection. Rest mibi SPECT was performed on a separate day, 1 h after a new injection of the same dose of radiotracer.

Analysis of SPECT. For each patient, six short-axis slices and three vertical long-axis slices were displayed and analyzed. As previously described (14), the left ventricle was divided into 47 segments, and each segment was scored on a four-point scale (from 1 = normal to 4 = “absence” of uptake). The visual analysis was performed by two observers with the assistance of the circumferential profile analysis of the short-axis slices. The apical portion was assessed only visually on the vertical and horizontal long-axis slices. An ischemic response was based on the presence of transient perfusion defect.

Quantitative coronary arteriography. All 35-mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical). The automated edge detection of the system has been validated and described elsewhere (15). A region of interest of 512 × 512 pixels was selected and digitized with a high fidelity charge-coupled device camera. The lumen edges were detected on the basis of a weighted sum of the first- and second-derivative function of the brightness profile of each scan line perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using the catheter tip as a scaling device. A computer-derived estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated center reference diameter. This technique is based on a computer-derived estimation of the original values over the analyzed region. The calculation is based on a first-degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment, followed by a translation to the 80th percentile level. All measurements were performed from end-diastolic frames with optimal vessel opacification.

Statistical analysis. All continuous variables are expressed as mean value ± SD. The agreement between echocardiography and SPECT was defined as the percentage of concordant diagnosis, and it was also assessed by calculating the kappa value and the corresponding 95% confidence intervals. Receiver operating characteristic curve analysis was used as an objective method for determining the power of the angiographic variables for the prediction of an abnormal exercise echocardiography and SPECT. Sensitivity and specificity were plotted against the whole range of measurements of a specific variable for determining the “best” cutoff point. The best cutoff point was defined as the intersection of the sensitivity/specificity curves. The sensitivity/specificity values at these cutoff points are reported as percent with the corresponding 95% confidence interval (CI).
Results

Exercise testing results. Mean maximal heart rate was 145 beats/min (range 120 to 190); 85% of the maximal age-predicted heart rate was not reached in eight patients. In four patients the exercise was stopped because of chest pain, and in another four for fatigue (in three of these last four echocardiographic results were positive). During the exercise test, angina occurred in 9 patients, and ST segment depression (horizontal or downsloping >1 mm) in 14.

Exercise echocardiography. New wall motion abnormalities were detected on the postexercise echocardiogram in 16 patients. The site of wall motion abnormalities was always consistent with the territory of the left anterior descending coronary artery.

Exercise SPECT results. Transient perfusion defects were present, all in the distribution territory of the left anterior descending coronary artery, in 19 patients. The agreement between echocardiography and SPECT for the diagnosis of myocardial ischemia is represented in Figure 1 (22 [70%] of 31, kappa value 0.42, 95% CI 0.10 to 0.74). Of the nine patients with discordant responses, six had positive SPECT and negative echocardiographic results. The median diameter stenosis and minimal lumen diameter in these six patients were 35% (range 30% to 53%) and 1.89 mm (range 1.12 to 2.26 mm), respectively.

Quantitative arteriography and exercise-induced myocardial ischemia. Quantitative coronary arteriography revealed a mean percent diameter stenosis of 52 ± 19 (range 30% to 100%; two patients had total occlusion). The diameter stenosis was <50% in 14 patients, 50% to 70% in 13 and >70% in 4. Mean minimal lumen diameter was 1.20 ± 0.58 mm (range 0 to 2.26). Faint collateral vessels were visible in the two patients with occluded arteries.

Sensitivity and specificity of the individual values of diameter stenosis and minimal lumen diameter for the correct classification of patients with and without exercise-induced myocardial ischemia are depicted in Figure 2 for echocardiography and in Figure 3 for SPECT. From these figures it can be observed that the “best” cutoff point of diameter stenosis (defined as the value at the cross point of sensitivity and specificity curves) for predicting a positive response during exercise was similar for echocardiography and SPECT (52% vs. 49%, respectively). However, the sensitivity/specificity cross point was slightly higher for echocardiography than SPECT (81% [95% CI 54 to 96] vs. 67% [95% CI 43 to 87]). Similar results were found considering the minimal lumen diameter, including a similar “optimal” cutoff (1.12 vs. 1.20 mm) and a trend suggesting a slightly higher sensitivity/specificity cross point for exercise echocardiography (81% [95% CI 54 to 96] vs. 74% [95% CI 48 to 90]).

In Figure 4, the receiver operating characteristic curves of quantitative coronary arteriography for the prediction of wall motion abnormalities and perfusion defects are separately represented. There is a clear trend showing that the areas below the receiver operating characteristic curves for the prediction of new wall motion abnormalities were larger than those for the prediction of transient perfusion defects. This observation suggests that these angiographic parameters are better related to the mechanical than to the perfusion marker of ischemia.

The accuracy of distal stenosis and minimal lumen diameter for new wall motion abnormalities was similar, because the areas below the respective receiver operating characteristic curves were not statistically different (93% vs. 95%).
Discussion

Although coronary artery disease comprises a continuous spectrum of obstruction severities, the diagnostic accuracy of noninvasive tests relies mostly on one arbitrary angiographic cutoff value to define "significant" disease. This "fuzzy" decision implies that some stenoses that are physiologically nonsignificant may be included in the definition of the presence of disease, and also that some physiologically significant stenoses may be classified as nonsignificant. Clearly, this is a crucial issue because one of the most important determinants of the sensitivity and specificity of noninvasive tests for the diagnosis of coronary artery disease is the definition of the angiographic reference (which variable and which cutoff value for each variable). In addition, many reports do not rely on quantitative angiographic assessment of coronary stenoses, which can be a major drawback of any study aiming at assessing the accuracy of any test for the diagnosis of coronary artery disease (1,16).

The present study. The aim of the present study was to assess the value of quantitative coronary arteriography for predicting an ischemic response to exercise echocardiography and mibi SPECT in a selected group of patients without previous myocardial infarction and isolated discrete mild to severe lesions in the proximal or midportion of the left anterior descending coronary artery. To address this problem, quantitative measurements of the coronary stenoses were obtained by quantitative coronary angiography, and the functional end point of the study was the ischemic response to symptom-limited exercise echocardiography and mibi SPECT, which were simultaneously applied in all patients. To assess the relation between coronary stenosis and exercise-induced ischemia over the whole range of obstruction severity, the receiver operating characteristic and the sensitivity/specificity curves from the percent diameter stenosis and minimal lumen diameter were analyzed. This approach allows the identification of the most efficient angiographic cutoff values for predicting an ischemic response to stress echocardiography and SPECT. Toward this aim, we used a utility function in which sensitivity and specificity are considered equally appropriate.

The present study provides new information because the few previous comparative studies between exercise echocardiography and perfusion scintigraphy (7–12) were confounded by the inclusion of patients with previous myocardial infarction or multivessel coronary disease. Further, to our knowledge no study included a homogeneous group with single-vessel left
anterior descending coronary artery disease, the functional significance of different degrees of stenosis severity was not explored, and in some studies the quantitative assessment of coronary angiograms was not appropriate.

The best angiographic cutoff values from diameter stenosis and minimal lumen diameter for predicting the functional outcome of exercise stress testing is similar; 3) quantitative coronary arteriographic measurements are slightly better related to echocardiographic than to scintigraphic results.

The "best" angiographic variable and cutoff values. The diagnostic accuracy of diameter stenosis and minimal lumen diameter was similar for the prediction of both exercise echocardiography and mibi SPECT. This is in contrast to previous studies suggesting that minimal lumen diameter is a better variable for characterizing the functional significance of coronary stenoses (17). This difference may be related to patient selection. For instance, Wilson et al. (18) found that, consistent with our results, diameter stenosis is a functionally meaningful variable in patients with discrete single-site coronary artery narrowing. It is likely that minimal lumen diameter is superior to diameter stenosis for the functional assessment of the coronary obstruction in patients with diffuse disease, which may be undetected or underestimated by measuring only the relative diameter differences (17,19). Consistent with our findings, recent data by Uren et al. (20) in patients with single-vessel disease and normal left ventricular function have shown that myocardial blood flow during adenosine- or dipyridamole-induced hyperemia is equally well correlated with diameter stenosis and minimal lumen diameter (inverse correlation with the percent of diameter stenosis and direct correlation with the minimal lumen diameter).

In the present study, the cutoff values that optimally separated patients with a normal from those with an ischemic response during exercise were defined as those corresponding to the cross point of the sensitivity/specificity curves (Fig. 2 and 3). They were 52% for diameter stenosis and 1.12 mm for minimal lumen diameter, using the echocardiographic end point. They were similar when mibi SPECT was applied (49% and 1.20 mm, respectively). These results are in agreement with the cutoff values found applying a similar statistical approach but utilizing different stress or imaging modalities such as exercise ECG (21) or dobutamine echocardiography (22) as functional end point.

Exercise echocardiography versus mibi SPECT. An important finding of the present study is that the results of exercise echocardiography are predicted by quantitative coronary arteriography at least as well as those of mibi SPECT. This can be concluded from inspection of the receiver operating characteristic and sensitivity/specificity curves. From the analysis of the receiver operating characteristic curves, the sensitivity and specificity for the prediction of a positive exercise echocardiographic response are slightly higher than those for the prediction of a positive mibi SPECT response during the whole range of measurements of both diameter stenosis and minimal lumen diameter (Fig. 4). This higher sensitivity and specificity of coronary angiography for the prediction of echocardiographic results is confirmed by the sensitivity/specificity curves (Fig. 2 and 3). Inspection of these curves allows the assessment of the sensitivity and specificity over the whole range of diameter stenosis and minimal lumen diameter, and the cross point represents the cutoff of the angiographic variables with the "optimal" sensitivity and specificity. In this specific case, it clearly appears that although the values of both diameter stenosis and minimal lumen diameter at the cross point were similar for exercise echocardiography and mibi SPECT, the sensitivity-specificity values at the cross point were slightly lower for mibi SPECT than for echocardiography, implying a less strict relation of coronary arteriographic measurements with scintigraphy than with echocardiography.

Several factors may explain the discrepancies between exercise echocardiography and mibi SPECT. Both imaging methods have limitations and pitfalls. Perfusion SPECT may lack optimal diagnostic accuracy for a variety of technical reasons, such as soft tissue attenuation, overlying abdominal viscera, ventricular hypertrophy, cardiac rotation or patient motion (23). Acquisition of echocardiographic stress images is strongly operator dependent, and with the postexercise acquisition some mild transient ischemia may be missed (24). Furthermore, SPECT perfusion imaging detects not only true myocardial ischemia but also malperfusion, which results in detection of stenosis of mild/moderate degree. This has been underscored in recent observations by Uren et al. (20), who found a decline of the coronary vasodilator reserve during adenosine- or dipyridamole-induced hyperemia in humans for moderate degrees of coronary diameter stenosis, starting from 40%, and an exhaustion of coronary reserve for stenoses greater than 80%.

It is uncertain which of these factors intrinsic to the two methods were of importance in our series. However, the results of the present study suggest that the "gray zone" for the prediction of exercise-induced myocardial ischemia from quantitative coronary angiography is smaller for echocardiography than for perfusion scintigraphy.

References

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