Integrated Evaluation of Relation Between Coronary Lesion Features and Stress Echocardiography Results: The Importance of Coronary Lesion Morphology

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OBJECTIVES
The aim of this study was to analyze, in the same group of patients, the relationship between multiple variables of coronary lesion and results of exercise, dobutamine and dipyridamole stress echocardiography tests.

BACKGROUND
Integrated evaluation of the relation between stress echocardiography results and angiographic variables should include not only the assessment of stenosis severity but also evaluation of other quantitative and qualitative features of coronary stenosis.

METHODS
Study population consisted of 168 (138 male, 30 female, mean age 51 ± 9 years) patients, on whom exercise (Bruce treadmill protocol), dobutamine (up to 40 mcg/kg/min) and dipyridamole (0.84 mg/kg over 10 min) stress echocardiography tests were performed. Stress echocardiography test was considered positive for myocardial ischemia when a new wall motion abnormality was observed. One-vessel coronary stenosis ranging from mild stenosis to complete obstruction of the vessel was present in 153 patients, and 15 patients had normal coronary arteries. The observed angiographic variables included particular coronary vessel, stenosis location, the presence of collaterals, plaque morphology according to Ambrose classification, percent diameter stenosis and obstruction diameter as assessed by quantitative coronary arteriography.

RESULTS
Covariates significantly associated with the results of physical and pharmacological stress tests included for all three stress modalities presence of collateral circulation, percent diameter stenosis and obstruction diameter, as well as lesion morphology (p < 0.05 for all, except collaterals for dobutamine stress test, p = 0.06). By stepwise multiple logistic regression analysis, the strongest predictor of the outcome of exercise echocardiography test was only percent diameter stenosis (p = 0.0002). However, both dobutamine and particularly dipyridamole stress echocardiography results were associated not only with stenosis severity - percent diameter stenosis (dobutamine, p = 0.04; dipyridamole, p = 0.003) - but also, and even more strongly, with lesion morphology (dobutamine, p = 0.006; dipyridamole, p = 0.0009). As all of stress echocardiography results were significantly associated with percent diameter stenosis, the best angiographic cutoff in relation to the results of stress echocardiography test was: exercise, 54%; dobutamine, 58% and dipyridamole, 60% (p < 0.05 vs. exercise).

CONCLUSIONS
Integrated evaluation of angiographic variables have shown that the results of dobutamine and dipyridamole stress echocardiography are not only influenced by stenosis severity but also, and even more importantly, by plaque morphology. The results of exercise stress echocardiography, although separately influenced by plaque morphology, are predominantly influenced by stenosis severity, due to a stronger exercise capacity in provoking myocardial ischemia in milder forms of coronary stenosis. (J Am Coll Cardiol 1999;33:717–26) © 1999 by the American College of Cardiology
coronary artery disease pathophysiology and clinical outcome (4,5).

Several studies have found a fair relation between coronary stenosis severity as determined by quantitative angiography variables (percent diameter stenosis, minimal luminal diameter) and the results of stress echocardiography (6–8). Also, it has been shown that integrated evaluation of the relation between dipyridamole stress echocardiography results and angiographic variables includes not only the assessment of stenosis severity but also the evaluation of plaque morphology (9). However, it is indecisive whether the relation between specific type of lesion morphology and dipyridamole echocardiography result may be extrapolated to the other physical or pharmacological forms of stress testing. Thus, the aim of this study was to analyze, in the same group of patients, the relationship between multiple variables of coronary lesion and the results of exercise, dobutamine and dipyridamole stress echocardiography tests.

METHODS

Study population. The initial group consisted of 191 consecutive patients scheduled for coronary angiography on whom exercise, dobutamine and dipyridamole stress echocardiography tests were performed. None of them suffered from congestive heart failure, severe congenital or valvular heart disease, or documented cardiomyopathy. The patients with severe hypertension (systolic pressure >200 mm Hg and diastolic pressure >120 mm Hg), recent malignant ventricular arrhythmia and severe asthmatic or chronic obstructive pulmonary disease were not considered for the study, since these conditions represent a contraindication to dobutamine and dipyridamole stress testing. Stress echocardiography tests were performed in random order within two to three days in patients on their prescribed antianginal therapy. Our institution’s human use committee approved the study, and the informed consent was obtained from all the patients.

Of this initial set of 191 consecutive patients, 23 patients were ruled out from further analysis because of the presence of multivessel coronary artery disease which would make correlation complex and uncertain. The results of exercise, dobutamine and dipyridamole stress echocardiography testing were analyzed in the remaining 168 patients (mean age 51 ± 9 years; range 28 to 71 years; 130 male, 38 female). Coronary stenosis, ranging from mild to complete obstruction of the coronary vessel, was found in 153 out of 168 patients. In 15 patients no identifiable lesion was found, thus the relation between stress echocardiography results and quantitative and qualitative angiographic features of coronary stenosis was restricted to 153 patients. Quantitative and qualitative parameters of coronary stenosis evaluated in the analysis included: particular stenotic coronary artery vessel, stenosis localization, presence of collateral circulation, obstruction diameter and percent diameter stenosis as determined by quantitative coronary arteriography and the type of coronary lesion morphology. Coronary lesion morphology was defined as simple: correspondent to Ambrose I and IIa classification, including lesions with smooth and regular borders without intraluminal filling defects, and complex: correspondent to Ambrose IIb and III classification, included lesions with irregular, rough borders, ulceration with or without intraluminal filling defects suggestive of thrombus, as well as long atherosclerotic lesions with severe narrowing in series (9,10). Of the 168 patients, 40 (24%) had a previous non-Q wave myocardial infarction, 44 (26%) had a Q-wave myocardial infarction, 73 (44%) had angina pectoris and 11 (7%) patients complained of atypical chest pain. Stress echocardiography tests were performed at least 14 days after myocardial infarction and at least 3 days after stabilization of clinical symptoms in patients who presented with unstable angina. In 89% of patients, the clinically prescribed antianginal medications (single or combined) were continued and were the same during each stress test. These consisted of nitrates in 130 (77%) patients, calcium antagonists in 68 (40%) patients, and beta-adrenergic blocking agents in 52 (31%) patients. Theophylline and caffeine-containing products were not allowed for at least 12 hours before the tests.

Stress protocols. Exercise testing was performed according to the maximal Bruce treadmill protocol. Criteria for interrupting the test were severe chest pain, development of marked ST segment depression, age-predicted maximal target heart rate, systolic hypotension (decrease in systolic blood pressure >20 mm Hg) or hypertension (increase in systolic blood pressure >220 mm Hg, and diastolic blood pressure >120 mm Hg), appearance of frequent or complex ventricular arrhythmia, exercise limiting dyspnea, fatigue, claudication or other noncardiac symptoms necessitating cessation of exercise.

Dobutamine was infused intravenously using a mechanical pump, starting at the dose of 5 mcg/kg/min for 3 min, increasing to 10, 20 and 30 mcg/kg/min at 3 min intervals, to a maximal rate of 40 mcg/kg/min administered over 5 min. Dipyridamole was infused intravenously at the dose of 0.56 mg/kg over 5 min, followed by 4 min of no dose, and then, if the test was still negative, 0.28 mg/kg over 2 min. The cumulative dose was therefore 0.84 mg/kg over 10 min. The infusions were stopped before reaching maximal dose for any of the following reasons: obvious echocardiographic positivity, progressive and severe angina accompanied by marked ST segment changes, symptomatic hypotension (decrease in systolic blood pressure >20 mm Hg accompanied by nausea, sweating, dizziness, etc.) or hypertension (same criteria as during exercise), severe ECG rhythm or conduction abnormalities or intolerable symptoms. Intravenous aminophylline (250 mg) and intravenous propranolol (0.5 mg) were available after dipyridamole and dobutamine infusions, respectively.

A 12-lead electrocardiogram and blood pressure recording were performed at baseline and thereafter at the end of
each stress protocol stage or before the premature cessation of the test. Electrocardiographic tracing was considered diagnostic for myocardial ischemia in the presence of ST segment horizontal or downsloping depression of at least 0.1 mV, 0.08 s after J point compared to baseline. Rate-pressure product was calculated by multiplying systolic blood pressure and heart rate. All electrocardiographic results were reviewed without the knowledge of clinical data or the results of echocardiographic or angiographic findings.

**Echocardiographic analyses.** Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position, before and immediately after exercise test and continuously before, during, and after dobutamine and dipyridamole infusion. At the end of each stage and when new wall motion abnormalities developed, all views obtained at baseline were imaged. Following the cessation of the tests, echocardiographic imaging was continued until the return of hemodynamic parameters and/or left ventricular wall motion to the basal state. Interpretable echocardiograms were obtained in all patients. In each patient the apical approach (two chamber, four chamber and five chamber views) as well as parasternal long- and short-axis views were utilized, depending on the patient’s visually most useful acoustic window. All echocardiograms were performed using a commercially available imaging system (Toshiba SSH60A; Diasonics). A stress echocardiography test was interpreted from the off line digitized videotapes (ImageView, ATL), having these images, at rest and peak stress pharmacological test, as well as rest and immediate post exercise test, displayed in split screen cine-loop mode. Two observers, unaware of the patient’s clinical data, angiography findings or other echocardiographic test results analyzed the videotapes. For the purpose of analysis the left ventricular walls were divided into a 16-segment model. Segmental wall motion was evaluated using the method by the American Society of Echocardiography (11) as: normal, hypokinetic, akinetic or dyskinetic. If a consensus in reading stress echocardiography study could not be reached, the judgment of a third observer was obtained. A stress echocardiography test was considered positive when new or worsening of preexisting wall motion abnormality was observed. Only echocardiographic criteria (a new wall motion abnormality) were considered as positive tests. We had previously reported a high level of inter- and intraobserver reproducibility for the part of the initial group of patients (12).

**Coronary angiography and angiographic analyses.** All the patients underwent selective coronary angiography using the Judkins technique, within seven days of the stress echocardiography tests. Multiple views of each coronary artery were obtained. For the purpose of analysis, after visual inspection of the coronary artery in all views, the frame of optimal clarity in the end-diastolic part of cardiac cycle, in the view best showing coronary stenosis, was selected. The image was digitized and analyzed with the quantitative coronary angiography imaging system (Medis CMS, Netherlands, software version 1.11) by an observer unaware of the patient clinical data and echocardiographic results. For the purpose of the analysis, we utilized percent diameter stenosis and obstruction diameter as quantitative parameters of stenosis severity. Inter- and intraobserver variability of quantitative coronary arteriography measurement of end-diastolic approach for 20 randomly assigned patients have been evaluated by mean signed difference (representing accuracy) between the repeated measurements ± standard deviations of these differences (representing precision) and correlation coefficient (13). For interobserver variability, the mean difference (accuracy) ± standard deviation (precision) was 0.01 ± 0.16 mm, 0.97 ± 3.30% and 1.9 ± 6.6 mm, for obstruction diameter, percent diameter stenosis and length of the lesion, respectively, and the correlation coefficient was 0.94, 0.97 and 0.66 for obstruction diameter, percent diameter stenosis and length of the lesion, respectively. For intraobserver variability, the mean difference (accuracy) ± standard deviation (precision) was 0.03 ± 0.19 mm, 0.75 ± 3.59% and 1.2 ± 7.2 mm for obstruction diameter, percent diameter stenosis and length of the lesion, respectively and correlation coefficient was 0.92, 0.96 and 0.62 for obstruction diameter, percent diameter stenosis and length of the lesion, respectively. Therefore, the length of the lesion was not observed in further analysis because of the suboptimal and not acceptable level of reproducibility (<0.80 correlation coefficient, and low accuracy and precision in absolute terms). Significant coronary artery stenosis was considered present when 50% diameter stenosis of at least one major coronary artery was observed. Stenosis location was evaluated by utilizing a simplified coronary tree schema with the left main coronary artery, left anterior descending, left circumflex and right coronary arteries divided into proximal, middle and distal segments (14). Diagonal, marginal and other branches were classified as distal (or middle) segments of left anterior descending and left circumflex, correspondingly. Utilizing quantitative coronary analysis equipment, magnification of the coronary segment of interest and qualitative angiographic evaluation was performed according to the Ambrose classification (10). The qualitative evaluation was performed independently by two observers, and, in case of disagreement, the decision was based on the judgment of the third more experienced observer (M.O.). Interobserver variability for plaque morphology evaluation was 91% while the intraobserver variability was 94%.

**Statistical analyses.** The data are expressed as mean ± SD. Continuous variables were compared using the analyses of variance and Newman–Keuls procedure; t test for two independent groups was used where appropriate. Dichotomous variables were compared using a chi-square (McNemar’s test for paired proportions). Calculations of sensitivity, specificity and diagnostic accuracy were calculated in the standard manner. A P value less than 0.05 was considered to be statistically significant. Logistic regression analysis based
on the maximum-likelihood estimate was used to evaluate the relation between angiographic variables and the results of stress echocardiography tests. Categorical stress echocardiography results were regarded as the dependent variable, and all other variables (particular vessel, stenosis location, presence of collaterals, percent diameter stenosis, obstruction diameter, lesion morphology, antianginal medication and presence of resting wall motion abnormality) were regarded as independent variables, appropriately classified as quantitative or categorical. To select covariates independently associated with stress echocardiography results, significant univariate predictors were reassessed by a forward stepwise multivariate analysis with values for inclusion and elimination set at $p < 0.05$. Also, in order to determine the best angiographic cutoff value for identification of the results of each stress echocardiography test, we have determined the point of the maximum difference in achieving sensitivity and specificity, respectively, based on the probability calculated out of McNemar’s test. This technique is independent of definitions of cutoff values. Ninety-five percent confidence intervals were calculated for comparison of predictive power of the best angiographic cutoff value for each stress test.

RESULTS

Angiographic characteristics. Significant one-vessel coronary artery disease ($\geq 50\%$ diameter stenosis) was present in 128 patients, in 25 patients coronary lesion was $< 50\%$ diameter stenosis and in 15 patients coronary lesion was not identified. The distribution of affected vessels was: left anterior descending $= 103$ patients, circumflex artery $= 20$ patients and right coronary artery $= 30$ patients. Proximal coronary lesion was identified in 74 patients (left anterior descending coronary artery $= 65$, left circumflex $= 4$, right coronary artery $= 5$), middle coronary lesion was identified in 76 patients (left anterior descending coronary artery $= 38$, left circumflex $= 16$, right coronary artery $= 22$), and distal coronary lesion was identified in 3 patients (all right coronary artery). The complete obstruction of the coronary vessel was present in eight patients. Distribution of coronary stenosis according to quantitatively assessed diameter stenosis was presented in Figure 1. Mean obstruction diameter was 1.09 $\pm$ 0.50 mm, and mean percent diameter stenosis was 64 $\pm$ 15%. Simple lesion morphology was present in 63 patients (I–28 patients; IIa–35 patients) and complex lesion morphology was found in 90 patients (IIb–73 patients; III–17 patients). Collateral circulation was present in 40 and absent in 113 patients.

Hemodynamics and feasibility. During exercise testing and dobutamine infusion all observed hemodynamic values (heart rate, systolic and diastolic blood pressure and rate-pressure product) increased significantly ($p < 0.01$), whereas during dipyridamole infusion only heart rate and rate-pressure product significantly increased ($p < 0.01$). By analysis of variance, heart rate, blood pressure and rate-pressure product reached significantly higher levels during exercise than during dobutamine, and also during dipyridamole (peak rate-pressure product: exercise, 268 $\pm$ 59; dobutamine 178 $\pm$ 58; dipyridamole, 132 $\pm$ 29 mm Hg xbs/min/100; $p < 0.01$ for all intergroup differences).

The feasibility of exercise, dobutamine and dipyridamole stress echocardiography tests were 93%, 97% and 99%, respectively ($p = NS$), i.e., only 2, 5 and 12 patients during dipyridamole, dobutamine, and exercise were considered to have nondiagnostic stress test (negative test in patients not reaching age-predicted heart rate, or not completing full pharmacological test). The incidence of significant side effects were highest (16 patients) during dobutamine infusion and included mainly nonsustained ventricular tachycardia and hypotension and/or bradycardia. Significant side effects during all three stress tests were well controlled by immediate cessation of the test or administration of specific antidotes.

Overall diagnostic value of stress echocardiography tests. The sensitivity of exercise stress echocardiography (83%) tests for identification of myocardial ischemia was higher than that of dobutamine (77%) and dipyridamole (61%) stress echocardiography ($p < 0.05$ for all intergroup differences). The new or worsening of preexisting wall motion abnormalities seen in these patients corresponded always to the territory of the affected coronary vessel. Specificity was highest for dipyridamole stress echocardiography (88%) than that of dobutamine (77%) and dipyridamole (79%) testing, but the difference did not reach statistical significance ($p = NS$). The diagnostic accuracy of stress echocardiography tests was as follows: exercise 82%, dobutamine 74% and dipyridamole 67% ($p < 0.05$ for all intergroup differences).

Relation between multiple variables of coronary lesion and stress echocardiography results. Among the angiographical characteristics which are presented in Table 1, covariates significantly associated with the results of physical and pharmacological stress echocardiography results included for all three stress tests presence of collateral circulation, quantitatively determined percent diameter stenosis.
and obstruction diameter, as well as lesion morphology (p < 0.05 for all, except collaterals for dobutamine stress test, p = 0.06). We have also analyzed in this manner, the value of previous myocardial infarction with resting wall motion abnormalities, as well as concomitant beta-blocker and calcium antagonist therapy during testing, but none of this clinical covariates were significantly associated with the outcome of stress test results (exercise: previous infarction, p = 0.83; beta-blocker therapy, p = 0.62; calcium antagonists, p = 0.74; dobutamine: previous infarction, p = 0.16; beta-blocker therapy, p = 0.39; calcium antagonists, p = 0.52; dipyridamole: previous infarction, p = 0.76; beta-blocker therapy, p = 0.11; calcium antagonists, p = 0.25). Stepwise multiple logistic regression analysis was used to identify the strongest parameter determining stress echocardiography results (Table 2). The strongest predictor of the outcome of exercise echocardiography test was only percent diameter stenosis (p = 0.0002, OR adjusted for other

<table>
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<td>3.64</td>
<td>73%</td>
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variables in the model 1.07). However, both dobutamine and particularly dipyridamole stress echocardiography results were associated not only with stenosis severity—percent diameter stenosis (dobutamine, p = 0.04, adjusted OR 1.03; dipyridamole, p = 0.003, adjusted OR 1.05) but also, and even more importantly, with lesion morphology (dobutamine, p = 0.006, adjusted OR 3.07; dipyridamole, p = 0.0009, adjusted OR 3.64).

As all of stress echocardiography results were significantly associated with percent diameter stenosis, in Figure 2 we have presented the relation between sensitivity and specificity for each of the angiographic indexes as a function of stenosis severity. The best angiographic cutoff value with 95% confidence intervals (CI) for each stress echocardiography test is presented.

![Figure 2](image.png)

**Figure 2.** Relation between the sensitivity (solid triangles), specificity (asterisks) and diagnostic accuracy (solid squares) of the exercise (A), dobutamine (B), and dipyridamole (C) stress echocardiography as a function of quantitatively assessed percent diameter stenosis (n = 153). The best angiographic cutoff value with 95% confidence intervals (CI) for each stress echocardiography test is presented.

DISCUSSION

The principal finding of this study is that the results of pharmacological stress echocardiography test for detection of myocardial ischemia are dependent not only on absolute stenosis severity, but also and even more importantly, on the morphological pattern of the lesion. Our results are emphasizing and extending the findings of the previous study (9) showing that dipyridamole as well as dobutamine exert more frequently myocardial ischemia in the patients with complex coronary lesion morphology. The results of exercise echocardiography test, although separately influ-
ence by plaque morphology, are predominantly influenced by coronary stenosis severity.

Relation between stress echocardiography results and lesion morphology. The mechanism of provoking myocardial ischemia of dipyridamole on one side, and dobutamine and exercise on the other, is different: dipyridamole is reducing myocardial supply through flow maldistribution phenomenon, while the exercise and dobutamine causes myocardial ischemia through a marked increase in myocardial oxygen demand (15–17). Due to the different mechanism of action, which may induce different degrees of myocardial supply-demand mismatch, the ischemic potential of the respective tests is different. The previous findings have shown that the diagnostic potential is higher for exercise, than dobutamine and dipyridamole (12,15,18). With appreciation that coronary stenosis severity is not the only variable of coronary stenosis, it is suggestive that ischemic threshold is not the same for simple and complex coronary lesions. In fact for any given stenosis severity, the ischemic threshold may be different and dependent not only on anatomic severity but also on morphologic characteristics. It was noted that in the presence of moderate reduction in coronary reserve, the flow maldistribution provoked by dipyridamole might not occur or might not be severe enough to induce subendocardial ischemia (18,19). Thus, dobutamine and particularly dipyridamole with a lower ischemic potential may not reach ischemic ceiling in the presence of simple lesion morphology, while exercise may achieve it due to the higher inherent ischemic potential. On the other side in patients with a complex lesion of similar severity, the ischemic ceiling may be reached by all three tests due to the lower ischemic threshold of the lesion.

Mechanism of ischemia. Arteriolar dilation induced by physical or pharmacological stress consequently increases blood flow through the coronary artery in order to provide balance between myocardial demand and supply. However, in the presence of coronary stenosis, an increase in flow is accompanied by a pressure fall across the stenosis, and from the fluid dynamics point of view the magnitude of these changes is mostly dependent on the tube diameter or, in this case, stenosis diameter. Thus, the sensitivity of diagnostic tests would depend on their own ischemic potential and stenosis severity. However, it is suggestive from our results that the coronary stenosis morphology may significantly influence the results of pharmacological stress testing. This may be explained partly by the previous report showing that complex coronary stenosis morphology are associated with more profound endothelial damage (20,21), i.e., loss of endothelial integrity in complex lesions will reduce local plaque vasodilatation properties increasing the pressure drop across the stenosis (22). In addition, by fluid dynamics, the pressure drop across the stenosis will be higher in presence of complex lesion morphology due to the higher energy loss in this type of lesion (23). Thus, the lower ischemic threshold of complex lesions may be the consequence of the higher pressure drop across this morphological type of lesions resulting from the combined biological (endothelium dependent) and mechanical factors.

Comparison to previous studies. The application of quantitative coronary arteriography has made it possible to objectively study angiographic images, and it has become the main methodological tool in a number of coronary artery disease investigations (24). Bartunek et al. (8) have shown that the magnitude of wall motion abnormalities induced by dobutamine infusion correlates well with angiographic indexes of stenosis severity even though a wide scatter was observed. However, they have not found any relation between qualitative descriptors of stenosis morphology and degree of dyssnergy. Also, Baptista et al. (7) in the study of relation between dobutamine-atropine stress echocardiography results and quantitative features of stenosis have presented a nice relation between them with the angiographic cutoff value best predicting the development of wall motion abnormalities of 52%. This is in concordance with our findings on dobutamine stress echocardiography test with angiographic cutoff point at 58% diameter stenosis, as the addition of atropine to dobutamine negative patients would identify less severe coronary stenosis. However, Heyman et al. (25) in patients with nonocclusive single-vessel disease, have not found association between complex type coronary stenosis and greater vulnerability to dobutamine-atropine induced ischemia. Most importantly, in the study comparing the dipyridamole stress echocardiography findings and qualitative features of the lesion (9), Lu et al. have found that dipyridamole sensitivity was associated with complex type coronary morphology, indicating that physiological consequences of a stenosis cannot always be predicted with a simple anatomic-geometric approach. The findings of our study are correspondent to their results, and even more, extrapolated to other investigated test modalities. Varga et al. (26) have confirmed the relation between complex lesion morphology and dipyridamole echocardiography test positivity. On the other hand, less severe stenosis was more frequently detected by dobutamine-atropine stress echocardiography (26). Differences to our results, in regard to dobutamine, may be related to addition of atropine in dobutamine negative patients not reaching target heart rate (in our study group only 14% of patients reached target heart rate during dobutamine and no additional atropine was administered), as well as different selection criteria (multivessel disease included) and smaller sample size (25,26).

We have shown that collateral circulation is univariately related significantly to the results of exercise and dipyridamole stress echocardiography and with borderline significance for dobutamine echocardiography. After vasodilatation, which may be induced either directly by vasodilating agent or indirectly by an increase in myocardial oxygen demand, the flow in the collateral circulation is decreased because the arteriolar bed of the nonstenotic artery com-
petes with the arteriolar bed of the stenotic artery that has already exhausted vasodilatory reserve (15,27). The findings of borderline significance of collateral circulation for dobutamine stress test may be explained by the significantly lower increase in myocardial oxygen demand (as expressed by rate-pressure product) during dobutamine infusion in relation to exercise. In addition, the lack of multivariate association between collateral circulation and stress echocardiography, particularly vasodilator, test results may be also due to the evidence that the majority of collateral circulation is not visible on an angiogram due to inherent resolution of the angiography. The findings of poor association of concomitant beta-blocker therapy with dipyridamole stress results may be explained by the nonexistence of significant resting and peak hemodynamic difference between patients on and off beta-blocker therapy—thus, a number of patients in this study group were most probable undermedicated with beta-blockers.

**Study limitations.** This was a retrospective analysis of our stress echocardiography data (12). However, the data acquisition was prospective and blinded to the present analysis in which the results of exercise, dobutamine and dipyridamole echocardiography testing were correlated to quantitative and qualitative features of coronary stenosis. Although we are routinely performing third generation stress echocardiography protocols (28–32), we have not included these tests in the study, because of: 1) methodological reasons—in that case the study population would be comprised of nonconsecutive and selected group of patients from two study protocols; 2) conceptual, and more important—the aim of the study was to evaluate the influence of various stenotic features on the results of stress echocardiography tests trying to understand the pathophysiological basis for development of myocardial ischemia during particular stress agent. Furthermore, the difference in sensitivity and diagnostic accuracy between dipyridamole and dobutamine observed in this study (linked to the skewed nature of the study population towards one-vessel coronary artery disease) evaporate with coadministration of atropine, as previously reported (30). However, further analysis is required to establish the relation between third generation stress echocardiography protocols, particularly dipyridamole-atropine and qualitative features of the coronary lesion.

It has been shown that quantitative arteriography analyses, apart from the technical issues, may show variability associated with the operators’ and patients’ dependent features (24). However, it is currently the most reproducible tool for analyses of angiograms, and with appreciation of the possible obstacles, many of operators’ dependent limitations may be overcome. Among basic anatomic parameters which were considered for analysis, including obstruction diameter, percent diameter stenosis and length, the length of the lesion was not observed in further analysis due to the unacceptable level of reproducibility (<80%), as well as the evidence that angiography systematically underestimates the size of the plaque. The qualitative features of coronary stenosis, although appreciated, have been routinely ignored in clinical classification of coronary stenosis probably due to the deficiency of quantitative classification criteria with respective variability (33). The qualitative assessment of plaque morphology was visual, but adequate level of inter- and intraobserver agreement has been presented, probably due to interpretation and visualization of coronary stenosis from quantitative coronary arteriography system.

The use of echocardiography positivity as an end point might have important impact on the results of pharmacological stress techniques, when such a response may be readily detected during examination, compared with exercise technique, when the patient is more likely to exercise to a symptomatic end point and then have ischemia identified after stress. This alone might explain the difference in sensitivity between exercise and other techniques and the absence of impact of stenosis morphology on exercise induced ischemia by multivariate analysis.

**Clinical implication.** It has been shown that the degree of arterial obstruction does not correlate with the risk for subsequent acute ischemic events (34), and the growing evidence indicates that the degree of coronary obstruction even precisely measured is just one, maybe not the most important, feature of coronary stenosis, and that plaque morphology as well as endothelial function and plaque composition are other significant determinants of coronary stenosis. Together, not by themselves, they determine the outcome of the coronary stenosis. We have shown in this group of patients with discrete one-vessel coronary stenosis that dipyridamole, as well as dobutamine, more frequently exert myocardial ischemia in the patients with complex coronary lesion morphology. The results of stronger stressor (exercise) are less, if at all, affected by stenosis lesion morphology due to the higher ischemic potential and due to a lack of echocardiography monitoring during exercise where the overshooting of ischemic threshold during exercise occurs in probably most of the patients. Thus, the findings of positive, particularly dipyridamole and dobutamine, stress echocardiography tests may suggest severe and complex coronary artery stenosis requiring expeditious further diagnostic evaluation as it has been shown that such lesions are more likely to undergo occlusion and myocardial infarction (35,36). On the other hand, exercise (or dobutamine-atropine [25,26]) stress echocardiography may identify less severe forms of coronary stenosis. Our results are indirectly supporting the concept that maybe it is not most important to detect geometrically significant stenosis but a complex one which may be troublesome in the follow up period. In expert hands, the results of stress echocardiography testing may actually provide subtle “master mind” algorithm for clinical evaluation and decision making.
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