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Exercise Testing

Supine Bicycle Echocardiography

Improved Diagnostic Accuracy and Physiologic Assessment of Coronary Artery Disease With the Incorporation of Intermediate Stages of Exercise

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Objectives The purpose of this work was to assess whether the incorporation of intermediate stages during supine bicycle exercise echocardiography (BEE) improves the accuracy of detection of coronary artery disease (CAD) through the evaluation of a biphasic response.

Background Exercise echocardiography allows cardiac imaging throughout exercise.

Methods Exercise echocardiography was performed in 104 patients (mean age 57 ± 11 years, 37 women), 91 of whom underwent coronary angiography. The BEE protocol started at 25 W with increments of 25 W every 3-min stage. Images were digitized at rest, 25 W, 50 W, and peak exercise. Two experienced observers and 1 less experienced observer interpreted rest and peak exercise images, with and without the intermediate stages.

Results Imaging during intermediate stages improved the sensitivity for detection of all individual vessel stenoses (78% vs. 58%, $p < 0.001$) and patients overall (94% vs. 74%, $p = 0.001$). The specificity was unchanged (all vessels: 83% vs. 81%, all patients: 64% vs. 60%). A change in left ventricular end-systolic volume from intermediate stage to peak exercise of >10% predicted CAD (sensitivity 94%, specificity 74%) and was more marked than changes observed from rest to peak exercise. The severity of coronary stenosis related to the double product achieved at the onset of ischemia during exercise ($r = -0.61$, $p < 0.001$) better than that at maximal exercise ($r = -0.31$, $p < 0.01$).

Conclusions During BEE, the acquisition and interpretation of intermediate stages of exercise in addition to peak exercise improves the detection of CAD and allows a better physiologic evaluation of the severity of coronary stenosis. (J Am Coll Cardiol 2007;50:1857–63) © 2007 by the American College of Cardiology Foundation

Exercise echocardiography is currently a well-established modality for the evaluation of patients with known or suspected coronary artery disease (CAD) (1,2). Compared with the post-treadmill approach, supine bicycle exercise echocardiography (BEE) offers the advantage of feasibility of imaging during exercise (3–6). Whether imaging during the various stages of exercise, in addition to peak exercise, has important implications is currently not known. While all laboratories use rest and peak exercise for interpretation (3–7), a minority acquire images during intermediate stages for optimizing image quality and cardiac monitoring (4,8) and, more recently, for the assessment of myocardial viability after myocardial infarction (9). We hypothesized that, during routine BEE, the incorporation of imaging during intermediate stages of exercise in addition to rest and peak exercise allows for improvement in the accuracy of BEE by detecting subtle ischemia through a biphasic response. This protocol may also permit a better prediction of the severity of CAD through the evaluation of the threshold at which ischemia occurs during exercise. Accordingly, the present study was conducted to assess the comparative accuracy of BEE, with and without imaging during intermediate stages of exercise, in the detection of CAD, and to evaluate whether an ischemic threshold identified with this imaging protocol relates to the severity of CAD by quantitative angiography.

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Methods

Study population. In a 2-year period, all patients who underwent BEE for the evaluation of CAD and coronary angiography within 3 months at The Methodist DeBakey Heart Center were eligible for enrollment. The study was

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Abbreviations and Acronyms

BEE = bicycle exercise echocardiography

CAD = coronary artery disease

LAD = left anterior descending coronary artery

LCX = left circumflex artery

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

RCA = right coronary artery

R-I-P = rest-intermediate stages-peak protocol

R-P = rest-peak protocol

WMSI = wall motion score index

approved by the Investigational Review Board of the Methodist Hospital. There were 91 patients, of whom 76 underwent BEE first and 15 underwent coronary angiography without revascularization before the BEE (time interval 36 ± 44 days). Thirteen volunteers without risk factors for CAD (age 45 ± 8 years) who underwent BEE without coronary angiography were also included and served as additional normals. These individuals were included and their studies read randomly, mixed with the other population, to help decrease bias in interpretation because of the high prevalence of CAD in patients undergoing coronary angiography. The total study group therefore consisted of 104 individuals (age 57 ± 11 years, 37 women).

Supine BEE. Echocardiography was performed using a Hewlett-Packard Sonos 5500 ultrasound system. A BEE bed was used (Medical Positioning, Inc., Kansas City, Missouri) with a capability of tilt to the left lateral position, as needed, to a maximum of 30° and head elevation to a maximum of 20° to optimize images (6). After obtaining the rest images from the standard parasternal and apical views, patients pedaled at constant speed beginning at a workload of 25 W and increasing by 25 W every 3-min stage. Images were digitized in a quad-screen at rest, stage I (25 W), stage II (50 W), and at peak exercise and were also recorded on videotape. If any of the myocardial segments was not well visualized at rest, 0.3 to 0.5 ml of echocardiography contrast (Optison, Mallinkrodt, Missouri) was injected intravenously followed by a 3 to 5 ml saline flush to optimize endocardial visualization during acquisition of all images. A symptom-limited protocol was used, stopping the exercise for intolerable symptoms and other safety end points (6).

Echocardiographic analysis. Images were interpreted by 2 experienced observers (>20 years experience) and 1 less experienced reviewer (recent Level 2 training) blinded to all clinical data. The interpretation was based on review of the digitized images, supplemented by review of videotaped images if needed. During the interpretation sessions, the images were prepared for the interpreter by an assistant who maintained the blind of patient identification. The digital workstation (Digiview, Digisonics Inc., Houston, Texas) also allowed masking the images of the intermediate stages in the quad-screen to allow interpretation of rest and peak (R-P) images only (Fig. 1, Online Video). All studies were first interpreted with R-P images only, in a random order. A few weeks later, they were reinterpreted in a random order by the same observer with all intermediate stages of exercise in addition to rest and peak images (R-I-P) (Fig. 1, Online Video).

Analysis and scoring of regional wall motion was performed per the recommendations of the American Society of Echocardiography (10). For either protocol, a normal response was defined as normal rest function with normal or hyperdynamic function during exercise, ischemia as the development of abnormal or worsening wall motion, and a fixed abnormality as a wall motion abnormality at rest without deterioration during stress. For the R-I-P protocol, progression of regional function during the intermediate stages was also noted. Ischemia was subclassified into a biphasic response (segments exhibiting improvement in the intermediate stages from normal or abnormal function at rest and then worsening function with higher stress levels)

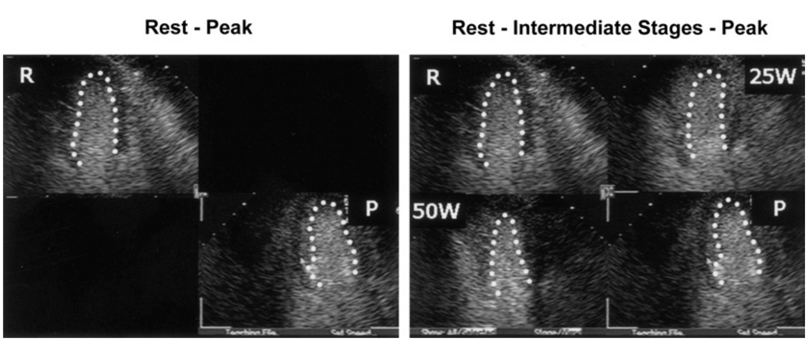

Figure 1 **Protocols of Interpretation of Rest, Intermediate Stages, and Peak Exercise and the Process of Blinding the Intermediate Stages**

Still images (and Online Videos) in the 2-chamber view at end-systole from a patient who was interpreted as having right coronary artery ischemia with bicycle exercise echocardiography without intermediate-stage images and as having, in addition, left anterior descending coronary artery ischemia with bicycle exercise echocardiography with intermediate stage. Note the smallest left ventricular end-systolic volume at 50 W (stage II) and the left ventricular dilatation at peak. This and the anterior ischemia are not as obvious if rest (R) and peak (P) images were only displayed.

Please see the Appendix for accompanying videos.

and worsening response (deterioration during stress without improvement in intermediate stages).

For global function, a wall motion score index (WMSI) was calculated (10). The simplified method of Tortoledo et al. (11) was used to determine left ventricular end-diastolic volume and left ventricular end-systolic volume (LVESV) (11) at various stages of exercise from which left ventricular ejection fraction (LVEF) was derived. This method has the advantage of incorporating parasternal views, thus avoiding foreshortened beats. To evaluate the power of changes in LVESV in detecting CAD, percent change in LVESV at peak stress was calculated as change from rest, as well as the change from the smallest end-systolic volume during the intermediate stage of exercise (best functional reserve).

For the purpose of comparison with coronary angiography, regional segments were matched to the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA) as previous described (6). Analysis was also performed in the distribution of the LAD and non-LAD territories, as the RCA and LCX territories frequently overlap.

Quantitative coronary angiography. Coronary angiography was performed in multiple projections using the standard Judkins technique. An independent experienced observer using the CASS system (Pie Medical Instruments, Maastricht, the Netherlands) quantitated the coronary angiograms. Significant coronary stenosis was defined as the presence of ≥50% stenosis in a major epicardial coronary artery.

Statistical analysis. Continuous data are presented as mean ± standard deviation, and categorical variables as percentages. Sensitivity, specificity, and accuracy for detection for CAD were derived for patients as well as coronary territories and compared between the 2 methods using McNemar test. Unpaired Student *t* tests and Mann-Whitney rank sum test were used to compare variables, with and without normal distribution, respectively, between patients with and without ischemia. A paired *t* test was used for comparison of percent change in LVESV (from baseline and from intermediate stage) in the same patients. Linear regression analysis was performed to examine the relation between the percent diameter stenosis and the double product at the occurrence of ischemia. Receiver operator curves for the detection of CAD were plotted for changes in LVESV. Significance was set at a p value of <0.05.

Results

Patient population. Of the 104 patients, 30 had 1-vessel disease, 24 had 2-vessel, 7 had 3-vessel, and 43 had no significant coronary artery lesions or were defined as normal. Two RCAs could not be evaluated at catheterization. The majority of patients (87.5%) had normal left ventricular wall motion at rest. The WMSI at rest averaged 1.01 ± 0.27. The electrocardiogram (ECG) at rest was normal in 62 patients (60%), and showed nonspecific ST-T changes in 28 (27%), Q waves in 11 (11%), and left bundle branch block in 3 patients (3%). Eighty-nine patients (86%) exercised 75 W or more. Contrast injection was used in 89 patients (86%). The echocardiographic images were of adequate quality with and without use of contrast in 96 patients and were technically difficult in 8 patients. Antianginal medications were not discontinued at the time of the imaging study; 30 patients were on beta-blocking agents and 11 on calcium antagonists.

Exercise testing. Thirty-seven percent of patients reached 85% of their age-predicted maximal heart rate, but 77% achieved a double product over 20,000 mm Hg × beats/min. Table 1 displays the hemodynamic findings during the exercise test. Eighty-two patients had no symptoms, 11 had atypical symptoms, and 11 patients had angina pectoris. No significant hypotension or ventricular tachycardia developed during stress. The stress ECG was positive for ischemia in 31 patients, yielding a sensitivity of 39%, a specificity of 88%, and an accuracy of 60%. In patients who achieved ≥85% target heart rate, the sensitivity was 68%, specificity was 76%, and accuracy was 71%.

Comparative accuracy of BEE protocols with and without intermediate exercise stages. The sensitivity, specificity, and accuracy for detection of CAD using both protocols are shown in Figure 2 and Tables 2 and 3. Compared with a R-P interpretation protocol, incorporation of intermediate imaging improved the sensitivity of detection of CAD of all coronary territories and all individual vessels affected; the specificity was unchanged. Results were similar if the few patients with a resting wall motion abnormality were excluded (sensitivity for all individual vessels 74%, specificity 84%).

Table 1 Hemodynamic Findings During BEE in 104 Individuals

	Rest	Stage I	Stage II	Peak
HR (beats/min)	69 ± 11	94 ± 14	105 ± 16	130 ± 21
Systolic BP (mm Hg)	141 ± 20	156 ± 26	160 ± 27	182 ± 30
Diastolic BP (mm Hg)	74 ± 12	82 ± 16	85 ± 22	88 ± 17
DP (beat/min × mm Hg × 10^3)	9.6 ± 2.1	14.6 ± 3.2	16.9 ± 4.1	23.7 ± 5.4

Data are expressed as mean ± SD.
BEE = bicycle exercise echocardiography; BP = blood pressure; DP = double product; HR = heart rate.

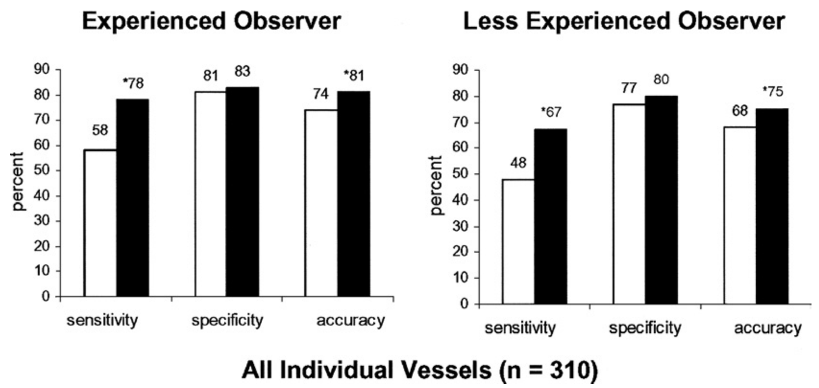

Figure 2 **Impact of Imaging Protocol on Diagnostic Accuracy of BEE**

Comparative diagnostic accuracy between rest-peak protocol (R-P) **(open bars)** and rest-intermediate stages-peak protocol **(solid bars)** during bicycle exercise echocardiography (BEE) in the detection of *all* vessels. *$p < 0.05$ versus R-P.

The change in interpretation of BEE in individual patients is shown in Figure 3. When relating these changes to angiographic findings, the diagnosis was completely and correctly changed with an R-I-P approach in 14 patients: 5 patients who had been called normal with R-P were diagnosed as having 1-vessel disease; 7 patients had a more correct assignment of the coronary distribution; and in 2 patients, the interpretation changed from 1-vessel disease to normal. Of the 15 patients who had been diagnosed as having 1-vessel disease with R-P images and were interpreted as multivessel disease with R-I-P protocol, 7 were correctly identified as multivessel disease. The majority of ischemic responses were biphasic (84% biphasic and 16% worsening response).

For interpretation by the less experienced observer, the sensitivity and accuracy in detecting all vessels with significant stenosis were also significantly improved with an R-I-P protocol while the specificity was similar (Table 3, Fig. 2). Using the R-I-P protocol, the sensitivity, specificity, and accuracy of experienced observers were slightly but not significantly higher than that of the less experienced observer (11%, 3%, and 6%, respectively).

Table 2 **Interpretation by Experienced Observers With or Without Intermediate Stages in Detection of CAD**

	Sensitivity (%) (R-P/R-I-P)	Specificity (%) (R-P/R-I-P)	Accuracy (%) (R-P/R-I-P)
LAD (n = 104)	64/83*	69/69	67/75
LCX (n = 104)	52/67	63/86	73/80
RCA (n = 104)	56/84*	90/91	81/89
Non-LAD (n = 102)	68/86	78/79	72/81
All vessels (n = 310)	58/78*	81/83	74/81*
All patients (n = 104)	74/94*	60/64	68/82*

*$p < 0.05$ versus supine bicycle exercise echocardiography without intermediate stage (R-P).
CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; R-I-P = supine bicycle echocardiography with intermediate stage.

Serial changes in ventricular function during exercise. Changes in ventricular volumes and LVEF from rest through the stages of exercise are shown in Table 4. In patients who developed ischemia, LVESV increased at peak exercise with a commensurate drop in LVEF ($p < 0.001$). Changes in LVESV were compared from rest to maximal exercise as well as from the best functional reserve to maximal exercise (Table 5). In ischemic patients, the change in LVESV from the intermediate stage to peak exercise was almost twice that observed from rest ($33.5 \pm 24.2\%$ vs. $17.5 \pm 19.9\%$; $p < 0.001$).

The accuracy of detection of CAD from changes in LVESV is depicted on the receiver operator curves in Figure 4. The area under the curve was slightly higher but comparable when using changes in LVESV from the intermediate stage to peak exercise or from rest to peak exercise. The best cutoffs for detection of CAD were a 0% change in LVESV from rest to peak exercise (sensitivity 92%, specificity 72%) and a 10% increase in LVESV from intermediate stage to peak exercise (sensitivity 94%, specificity 74%).

Relation of ischemic threshold during exercise to coronary stenosis severity. A significant inverse relation was observed between the double product of systolic blood

Table 3 **Interpretation by Less Experienced Observer With or Without Intermediate Stages in Detection of CAD**

	Sensitivity (%) (R-P/R-I-P)	Specificity (%) (R-P/R-I-P)	Accuracy (%) (R-P/R-I-P)
LAD (n = 104)	64/79	69/68	67/72
LCX (n = 104)	28/53	81/86	64/76
RCA (n = 104)	48/64	79/83	72/78
Non-LAD (n = 102)	60/71	74/77	68/75
All vessels (n = 310)	48/67*	77/80	68/75*
All patients (n = 104)	69/85	55/55	64/73

*$p < 0.05$ versus R-P.
Abbreviations as in Table 2.

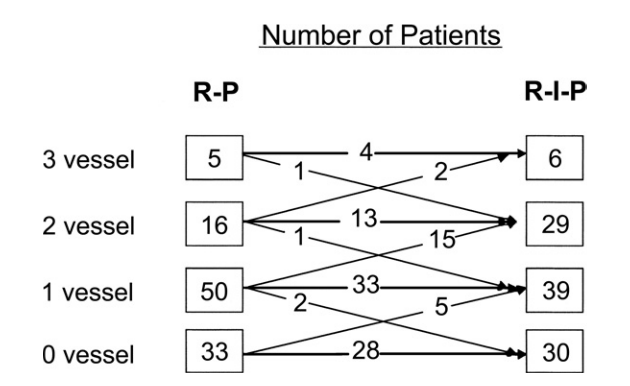

Figure 3 **Changes in Interpretation of BEE With Incorporation of Intermediate Stages of Exercise**

Individual changes in interpretation of bicycle exercise echocardiography (BEE) between the 2 protocols are shown. R-P = rest-peak protocol; R-I-P = rest-intermediate stages-peak protocol.

pressure and heart rate at the time of ischemia in the intermediate stages and percent coronary stenosis ($r = -0.61$, $p < 0.001$). This was observed with either coronary territory (Fig. 5). In the smaller group of patients on beta-blockers, the relation was maintained ($r = -0.87$). In contrast, the double product at maximal exertion had a poor relation to the severity of stenosis ($r = -0.31$, $p < 0.01$).

Discussion

This study demonstrates for the first time the importance of acquisition and interpretation of intermediate stages of exercise in the evaluation of CAD when using exercise echocardiography. By evaluating myocardial contractile reserve serially during stress, detection of ischemia is improved without a loss in specificity, for experienced and less experienced observers. Furthermore, this approach allows the assessment of the ischemic threshold during stress—an indicator of coronary stenosis severity.

Table 4 **Comparison of Selected Echocardiographic Variables Between Patients With and Without Ischemia**

	No Ischemia	Ischemia	p Value
LVEF (%)			
Rest (n = 32 vs. 72)	59 ± 9	58 ± 8	0.538
SI (n = 31 vs. 72)	60 ± 9	60 ± 9	0.768
SII (n = 27 vs. 72)	63 ± 10	61 ± 9	0.093
Peak (n = 32 vs. 72)	65 ± 11	55 ± 11	<0.001
LVEDV (ml)			
Rest (n = 32 vs. 72)	121 ± 16	121 ± 24	0.992
SI (n = 31 vs. 72)	119 ± 16	123 ± 24	0.406
SII (n = 27 vs. 72)	120 ± 17	123 ± 22	0.563
Peak (n = 32 vs. 72)	119 ± 19	124 ± 25	0.282
LVESV (ml)			
Rest (n = 32 vs. 72)	48 ± 12	49 ± 18	0.473
SI (n = 31 vs. 72)	46 ± 13	46 ± 17	0.361
SII (n = 27 vs. 72)	42 ± 13	47 ± 16	0.301
Peak (n = 32 vs. 72)	40 ± 19	57 ± 20	<0.001

LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SI = stage I of exercise (25 W); SII = stage II of exercise (50 W).

Table 5 **Comparison of Changes in LVESV From Rest and Smallest LVESV During Exercise to Maximal Exercise Between Patients With and Without Ischemia**

	No Ischemia	Ischemia	p Value
Rest to maximal exercise			
Changes in LVESV (ml)	−8.0 ± 15.4	8.0 ± 9.7	<0.001
Percent change in LVESV (%)	−17.3 ± 29.0	17.5 ± 19.9	<0.001
Intermediate stage to maximal exercise			
Changes in LVESV (ml)	−1.3 ± 12.0	13.2 ± 9.9	<0.001
Percent change in LVESV (%)	−5.5 ± 24.8	33.5 ± 24.2	<0.001

LVESV = left ventricular end-systolic volume.

Detection of ischemia with BEE. Compared with post-treadmill exercise, BEE offers the advantage of imaging during exercise in addition to peak exercise (3–7). We have previously demonstrated the comparative accuracy of detection of myocardial ischemia using treadmill exercise and BEE (6). The comparison was performed using rest and maximal exercise stages alone. The accuracy was similar, but ischemia was more extensive during BEE. In the present study, the impact of acquisition and interpretation of intermediate stages of exercise is highlighted. An improvement in detection of CAD was noted by incorporating information from the gradual contractile reserve: whereas in a normal response, a gradual improvement in regional and global function occurs along with a decrease in LVESV, the development of ischemia is heralded by an initial improvement followed by a gradual decrement in function—the biphasic response. Although this term has been used mostly in the assessment of myocardial viability, the present study emphasizes its importance in the detection of ischemia when regional function is also normal at rest. This methodology has been used implicitly in pharmacologic stress testing (display of incremental stages of stress) and in evaluation of myocardial viability with pharmacologic testing or bicycle exercise (9,12–16). The improvement in sensitivity observed in the present study is most likely because of the easier interpretation of serial incremental changes in wall motion as opposed to relying on 1 stage only at peak exercise, where subtle abnormalities can be missed by omitting an intermediate, hypercontractile stage. In fact, the majority of ischemic territories were detected by the presence of a biphasic response (92 of 110 ischemic territories or 84%), starting with normal function at baseline. Although the majority of improvement in detection of CAD was in the identification of additional ischemic territories in patients already labeled as ischemic, there was a change in sensitivity in 20% of patients with CAD whose ischemia was either missed

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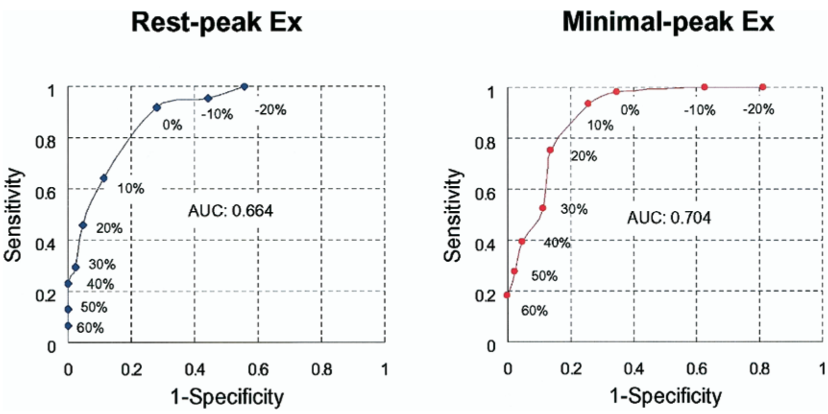

Figure 4 **Receiver-Operator Curves of Changes in LVESV During BEE and Detection of CAD**

Graphs showing sensitivity and specificity according to various cutoff values of percent change of left ventricular end-systolic volume (LVESV) for the detection of coronary artery disease (CAD). **(Left)** Percent change in LVESV from baseline to peak stage. **(Right)** Percent change from smallest LVESV in intermediate stages to peak exercise (Ex). AUC = area under the curve; BEE = bicycle exercise echocardiography.

(8% completely de novo) or misclassified by coronary distribution (12%). Importantly, the increase in sensitivity was observed by both the experienced and less experienced observers.

Changes in LVESV were also helpful in the assessment of CAD. The best cutoff for detection of CAD was a "no change" (flat response) in LVESV from rest to peak exercise. Evaluating change in LVESV from its smallest volume during intermediate stages of exercise to peak exercise (best contractile reserve) provided similar accuracy but yielded a larger change in LVESV in ischemic patients, and thus possibly an easier difference to discern during a qualitative interpretation.

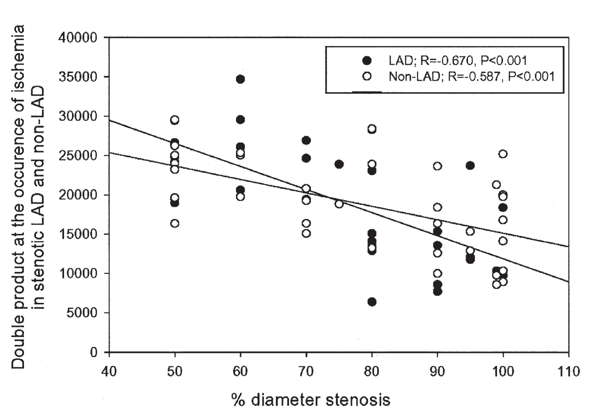

Figure 5 **Double Product at the Occurrence of Ischemia Versus Percent Coronary Stenosis**

Correlation between double product of systolic blood pressure and heart rate at the occurrence of ischemia and percent diameter stenosis in the 34 patients with left anterior descending coronary artery (LAD) stenosis and 38 patients with non-LAD stenosis.

Prediction of the severity of coronary stenosis. Evaluation of changes in myocardial function during graded pharmacologic stress testing with either dobutamine or dipyridamole has been related to the severity of the coronary stenosis (13,14,17). In a study evaluating patients with single-vessel disease and BEE where exercise was stopped at the onset of ischemia, Garot et al. (18) demonstrated that the ischemic threshold during exercise also relates to the severity of stenosis. The present study extends these observations to patients undergoing symptom-limited exercise and shows that the ischemic threshold in patients with single or multivessel disease relates inversely to the severity of coronary stenosis, better than at peak exercise. Several factors modulate this relation, however, beyond the epicardial stenosis, including the presence of collateral circulation, its vasodilating capacity, as well as ventricular diastolic pressure, which explain the modest relation observed (19). Nonetheless, the development of ischemia at low level exercise as assessed by continuous monitoring during bicycle exercise heralds severe coronary stenosis and likely worse prognosis.

Advantages and limitations. The majority of patients had normal wall motion at rest. In patients with extensive wall motion abnormalities, detection of CAD is not an issue, but viability is the question. The high ultimate sensitivity and moderate specificity observed reflects the current post-testing referral bias for coronary angiography but does not invalidate the comparative accuracy of both protocols. The high usage of contrast echocardiography for enhancement of endocardial border definition reflects our practice of optimizing image quality at every stage for better interpretation. We took advantage of digital blinding of the images to test our hypothesis in the same patients and in the same exercise test, eliminating the effect of these potentially confounding variables.

Conclusions

During BEE, the acquisition and interpretation of images during the intermediate stages of exercise, in addition to those at peak exercise, improve the detection of CAD and allow a physiologic assessment of the severity of coronary stenosis. The better diagnostic accuracy is seen in both experienced and less experienced observers. The change in LVESV during exercise is a useful parameter for the detection of CAD.

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APPENDIX

For accompanying videos to Figure 1, please see the online version of this article.