Relative Value of Isotonic and Isometric Exercise Radionuclide Angiography to Detect Coronary Heart Disease

MONTY M. BODENHEIMER, MD, FACC, VIDYA S. BANKA, MD, FACC,
JAI B. AGARWAL, MD, FACC, WILLIAM S. WEINTRAUB, MD, FACC,
RICHARD H. HELFANT, MD, FACC

Philadelphia, Pennsylvania

Isotonic and isometric stress have both been used in combination with radionuclide angiography to detect coronary heart disease. In view of the marked differences in these two forms of exercise and their relative advantages and disadvantages from a physiologic and a technical standpoint, these two techniques were compared in the same group of 48 patients undergoing diagnostic cardiac catheterization. All patients underwent first pass radionuclide angiography using a multicrystal camera at rest, during handgrip exercise and maximal bicycle exercise. Of the 48 patients, 28 had coronary artery disease and 20 had normal coronary arteries. Bicycle exercise resulted in a significantly higher rate-pressure product. Changes in global ejection fraction during handgrip exercise did not distinguish patients with or without disease. Eighty-two % of the patients with coronary artery disease showed an increase of less than 5 units in global ejection fraction during bicycle exercise. However, this criterion resulted in a low specificity of 30% in the patients with normal coronary arteries. In contrast, assessment of regional ejection fraction during bicycle exercise showed a sensitivity of 75% and a specificity of 65%. Handgrip exercise yielded a similar sensitivity of 68%, but the specificity was only 50%.

Thus, in patients without evidence of severe left ventricular dysfunction at rest, upright bicycle exercise combined with radionuclide angiography and analysis of regional ejection fraction provides a more optimal combination of sensitivity and specificity compared with assessment of global ejection fraction or the use of isometric handgrip exercise.

Exercise radionuclide angiography is being increasingly used to diagnose coronary artery disease (1,2). However, the type of exercise employed and the diagnostic criteria used for test interpretation differ. Borer et al. (3) and others (4–7) used isotonic exercise with the primary diagnostic variable being a change in ejection fraction. Recent studies confirmed the sensitivity but raised questions about the specificity of this variable (6,7). In our own laboratory as well as others, isometric exercise was used with analysis of regional wall motion as the primary criterion for a positive or negative test result (8,9). Preliminary reports from several laboratories showed variable results when isometric and isotonic exercise were compared (9–12).

In view of the inherent physiologic and technical differences, we compared these two exercise and interpretative formats in the same group of patients undergoing diagnostic cardiac catheterization and coronary arteriography. In order to determine the utility of these formats in a relatively more difficult diagnostic group, we limited the study population to those with no pathologic Q waves on the standard electrocardiogram and an ejection fraction at rest of 50% or more.

Methods

Study patients. Forty-eight patients admitted to our institution for diagnostic cardiac catheterization and coronary angiography as part of an evaluation for coronary heart disease fulfilled the following criteria and were entered into the study: 1) absence of pathologic Q waves defined as a Q wave of 0.04 second or more in lead aVF or V_1 to V_6 on the standard 12 lead electrocardiogram; 2) an ejection fraction of 50% or more determined with radionuclide angiography at rest; 3) absence of congenital or valvular (aortic or mitral, or both) heart disease and; 4) no administration of nitrates on the day of the study. A detailed history was also obtained to determine the intake of other cardiotonic medications, including beta-adrenergic blocking agents, which were discontinued at least 24 hours before the study Of the 48 patients, 36 were

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Address for reprints: Monty M Bodenheimer, MD, Division of Cardiology, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042.

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men and 12 were women; 28 had coronary artery disease and 20 had normal coronary arteries. The average age (± standard deviation) of the patients with coronary artery disease was 52 ± 9 years and of those with normal coronary arteries it was 50 ± 13 years. Of the 28 patients with coronary artery disease, 6 had single vessel disease, 14 had two vessel disease and 8 had three vessel disease.

Radionuclide angiography. All patients underwent radio-nuclide angiograms both at rest and during supine isometric handgrip exercise. For bicycle ergometry, a control study was performed in the upright position and during upright exercise. All studies were performed within 1 week of each other.

All radionuclide angiocardiograms were obtained using a computerized multicrystal scintillation camera (Baird Atomic System 77) and a 1 inch (2.54 cm) thick parallel hole collimator. After administration of 200 mg of potassium perchlorate, the patient was positioned in the right anterior oblique view and 12 to 18 mCi of technetium-99m pertechnetate in a volume less than 0.7 ml was rapidly administered into an antecubital vein and flushed with 10 to 15 ml of 5% dextrose in water to obtain a bolus injection. Counts were recorded at 40 frames/s (0.025 second intervals) during the "first pass" of the isotope. All data were recorded on computer disc for processing and magnetic tape for long-term storage.

Isometric handgrip exercise was performed in the following manner. The patient was asked to squeeze a hand dynamometer (CH Stoelting and Company) to the maximal extent possible and maintain contraction at one-third of the predetermined maximum for 3 to 4 minutes while blood pressure and heart rate were monitored (8). Care was taken not to allow the patient to perform a Valsalva maneuver. Before termination of handgrip exercise and after an increase in systolic pressure of greater than 20 mm Hg had been obtained, a background frame was collected, a second injection of pertechnetate was administered and a radionuclide angiogram was recorded. Chest pain or serious arrhythmias did not occur during handgrip exercise in any of the patients. Data acquisition required less than 20 seconds for each injection.

Bicycle ergometry was performed using a mechanically braked bicycle ergometer (13). The patients exercised on a bicycle ergometer at an initial zero load (< 30 seconds), and the work load was progressively increased every 2 minutes until maximal predicted heart rate, chest pain or severe 3 mm or greater ST segment depression or elevation occurred. Systemic blood pressure and electrocardiogram were monitored every minute during and after exercise. At peak exercise and before termination of exercise, a background frame was collected, a second injection of pertechnetate was rapidly administered and a radionuclide angiogram was recorded. In preliminary studies (not part of those with the present group of patients), we found that the rapid respiration associated with isotonic exercise is a significant cause of extraneous cardiac motion. Therefore, all patients practice an 8 to 10 second period of cessation of respiration during bolus transit, but special care is taken to avoid a Valsalva maneuver. This has resulted in a significant decrease in cardiac motion as confirmed by the ability to superimpose the end-diastolic images from sequential cardiac cycles.

Cardiac catheterization. This procedure was performed using standard techniques. Biplane left ventriculography was performed in the 30° right anterior and 60° left anterior oblique projections by injecting 30 to 40 ml of meglumine diatrizoate (Renografin-76) into the left ventricle. Selective coronary cinearteriography was performed in multiple views using the Judkins or Sones technique. Hemodynamic values were monitored and recorded on an Electronics for Medicine oscillographic recorder.

Analysis of data. All radionuclide angiographic data were processed as previously described from our laboratory (10,13). For the handgrip and bicycle studies, the background frame obtained at peak exercise immediately before the second injection was used to correct for preexisting counts. The study was viewed in a serial format on an oscilloscope. Frames of data containing the left ventricle were displayed and, using a zone grid representing the individual crystals, a region of interest comprising the left ventricle was selected and a time-activity curve generated. The peaks (diastole) and valleys (systole) were used to derive a computer-generated representative cycle, global left ventricular ejection fraction and end-diastolic and end-systolic frames.

A computer-derived image of regional ejection fraction was based on the formula CD − CS/CD − b (where CD = counts in diastole, CS = counts in systole and b = background). The computer-derived end-diastolic and end-systolic images were used to derive an image of stroke counts. This frame was divided by the background-corrected end-diastolic frame. The image thus obtained represents the relative contribution to ejection fraction of different zones of the left ventricle. To help localize abnormalities, a computer-derived end-diastolic perimeter was added to the image of relative regional ejection fraction. The left ventricle was further divided into anterior and inferior halves along the line from the mid point to the aortic valve plane to the apex. A relative decrease of at least 25% (a four color shift) involving one-third by area of either the anterior or inferior zone was considered indicative of an abnormal regional ejection fraction (10,13). This criterion was based on a previous series of patients in which it best separated a normal from an abnormal response (13).

The severity of a coronary lesion was assessed by comparing the diameter of the lesion with the diameter of the vessel immediately proximal to it. The obliquity showing the maximal decrease in diameter was selected for analysis in each case. Coronary artery narrowing of less than 50% of the luminal diameter was considered insignificant for the purposes of this study.

Exercise-induced changes in the ST segment were considered positive if 1.0 mm horizontal or downsloping changes were seen. Changes in ejection fraction induced by handgrip and bicycle exercise were correlated with the results of coronary arteriography. An increase in global ejection fraction of 5 or more absolute units was considered a normal response to bicycle exercise. In addition, results of analysis of changes in relative regional ejection fraction during handgrip and bicycle exercise were correlated with the results of coronary arteriography. Bicycle radionuclide angiography was performed simultaneously with acquisition of exercise electrocardiographic data; thus, the bicycle radionuclide data were also correlated with changes observed in the ST segment.

Statistical analysis. All data were analyzed using analysis of variance or a comparison of proportions wherever appropriate. All data are expressed as mean ± standard deviation.

Definition of terms used in the study:

Sensitivity = True positive/True positive + False negative

Specificity = True negative/True negative + False positive

Predictive value of a positive test (PV+) = True positive/True positive + False positive

Predictive value of a negative test (PV−) = True negative/True negative + False negative

Results

Effect of exercise on heart rate and blood pressure. Table 1 summarizes the changes in heart rate, systolic pressure and heart rate–systolic pressure product occurring during exercise. As expected, isometric handgrip resulted in a significant increase in systolic pressure both in patients without (n = 20) and with (n = 28) coronary artery disease. These changes were similar to those seen with bicycle exercise. In contrast, handgrip exercise resulted in small, albeit significant, increases in heart rate compared with bicycle exercise, resulting in large differences in the attained rate-pressure product.

Global ejection fraction. *Rest ejection fraction.* There was no difference in ejection fraction at rest between the patients with and without coronary heart disease (Table 2). Comparison of the ejection fraction at rest obtained supine before handgrip exercise with the rest ejection fraction obtained upright before bicycle exercise showed no significant difference. The average difference between supine and upright ejection fraction for the abnormal group was 1.6 ± 12.1% and for the normal patients 1.05 ± 10.0%.

Exercise ejection fraction. During isometric handgrip exercise there was a significant decrease in global ejection fraction in patients with and without coronary artery disease (Table 2). Similarly, bicycle exercise resulted in a significant decrease in global ejection fraction ($p < 0.01$) in patients with coronary artery disease. In contrast, ejection fraction remained unchanged in those with normal coronary arteries.

Table 1. Comparison of Effect of Exercise on Heart Rate, Systolic Pressure and Rate-Pressure Product

	Handgrip	Bicycle Ergometry
Patients with coronary artery disease		
Heart rate (beats/min)		
Rest	69 ± 12	74 ± 14
Exercise	83 ± 12*	134 ± 21*
Systolic pressure (mm Hg)		
Rest	128 ± 21	121 ± 17
Exercise	166 ± 24*	178 ± 30*
Rate-pressure product (beats·mm Hg/min)	13,599 ± 3,284	23,131 ± 6,732†
Patients with normal coronary arteries		
Heart rate (beats/min)		
Rest	71 ± 13	73 ± 11
Exercise	87 ± 16*	145 ± 21*
Systolic pressure (mm Hg)		
Rest	131 ± 17	117 ± 13
Exercise	174 ± 26*	187 ± 27*
Rate-pressure product (beats·mm Hg/min)	15,360 ± 3,481	26,701 ± 5,167†

Data are expressed as mean values ± standard deviation
*$p < 0.001$ (exercise compared with rest). †$p < 0.001$ (bicycle exercise compared with handgrip)

Table 2. Comparison of Effect of Exercise on Global Ejection Fraction (%)

	Handgrip	Bicycle Ergometry
Patients with coronary artery disease		
Ejection fraction		
Rest	68 ± 10	68 ± 11
Exercise	60 ± 10	57 ± 13
Patients with normal coronary arteries		
Ejection fraction		
Rest	70 ± 8	71 ± 10
Exercise	63 ± 13	69 ± 13

Data are expressed as mean values ± standard deviation
$p < 0.01$ (exercise compared with rest)

However, the change in ejection fraction during bicycle exercise could not be used to separate a normal from an abnormal response (Table 3). Thus, of the 28 patients with coronary artery disease, 23 showed either no change or a decrease in global ejection fraction for a sensitivity at this level of 82%. However, of the 20 patients with normal coronary arteries, only 6 showed an increase in ejection fraction of 5 or more absolute units for a specificity of 30%. With this criterion, predictive value of a positive test during bicycle exercise was 62%. Similarly, the change in ejection fraction during handgrip exercise was not diagnostic.

In patients without coronary disease, the ejection fraction response to bicycle exercise was dependent on the value at rest. In all 10 patients with normal coronary arteries and an ejection fraction of 70% or more, ejection fraction failed to increase by 5 units or more. In contrast, in 6 of 10 patients with a baseline ejection fraction of 50 to 69%, ejection fraction increased by 5 units or more.

Regional ejection fraction. Exercise-induced changes in relative regional ejection fraction (Table 4) resulted in sensitivities of 68% for handgrip and 75% for bicycle exercise compared with 54% for exercise-induced ST segment changes (Fig. 1). Specificity of regional ejection fraction changes during handgrip was 50%. In contrast, analysis of regional ejection fraction during bicycle exercise had a specificity of 65% ($p < 0.05$ using Fisher's exact test) (Fig. 2).

Table 3. Change in Absolute Global Ejection Fraction During Exercise

	Change in Ejection Fraction (in absolute units)				
	< −10	−5–9	0–4	5–9	>10
Patients with coronary artery disease					
Bicycle (n)	14	5	4	3	2
Handgrip (n)	10	7	9	2	0
Patients with normal coronary arteries					
Bicycle (n)	7	3	4	2	4
Handgrip (n)	7	5	7	1	0

n = number of patients

Table 4. Effect of Type of Exercise on Relative Regional Ejection Fraction

	Coronary Disease (n = 28)		Normal Coronary Arteries (n = 20)	
	Bicycle		Bicycle	
	Neg.	Pos	Neg	Pos
Handgrip				
Negative	4	5	8	2
Positive	3	16	5	5

n = number of patients. Neg = negative. Pos = positive

The relatively high specificity of exercise-induced ST segment changes of 90% is reflected in a predictive value of a positive response of 88% compared with 75% for regional changes in ejection fraction with bicycle exercise (Table 5). However, the low sensitivity of exercise-induced ST changes resulted in the lowest predictive value of a negative test of 50% compared with 65% for bicycle exercise regional ejection fraction changes (Table 5).

Bicycle exercise allows for simultaneous acquisition of electrocardiographic and radionuclide angiographic data. Table 6 shows the effect of combining results of the exercise-induced ST segment changes and regional wall motion. In 13 patients with a concordant abnormal response, all had coronary artery disease. However, of 16 patients with concordant normal studies, 5 had coronary artery disease and 11 patients did not. Of the five patients with coronary artery disease, two had one vessel, two had two vessel and one had three vessel disease.

Discussion

Experimental studies have shown that abnormalities of contraction are an almost immediate result of myocardial ischemia (14). This has led to the use of exercise combined with radionuclide angiography to detect noninvasively any underlying obstructive coronary artery disease. Borer et al. (3) found improved sensitivity and specificity for radionuclide angiography during bicycle exercise compared with exercise-induced abnormalities in the ST segment. Subsequently, several study groups (4–7) reported similar results.

Methodologic considerations. In our own laboratory, we used isometric handgrip exercise as an alternative approach to isotonic bicycle exercise. From a technical standpoint, isometric exercise has certain advantages. The patient is lying supine, and because only the arm is actively involved, motion artifact is minimal. Also, increases in heart rate (Table 1) are less marked. These factors increase the number of samples that can be obtained, optimizing the ability of the imaging technique to steadily record rapid dynamic changes. In contrast, isotonic exercise, associated with vigorous patient effort and higher heart rates, places a greater burden on the technical limits of current imaging techniques.

Physiologically isotonic exercise, however, clearly re-

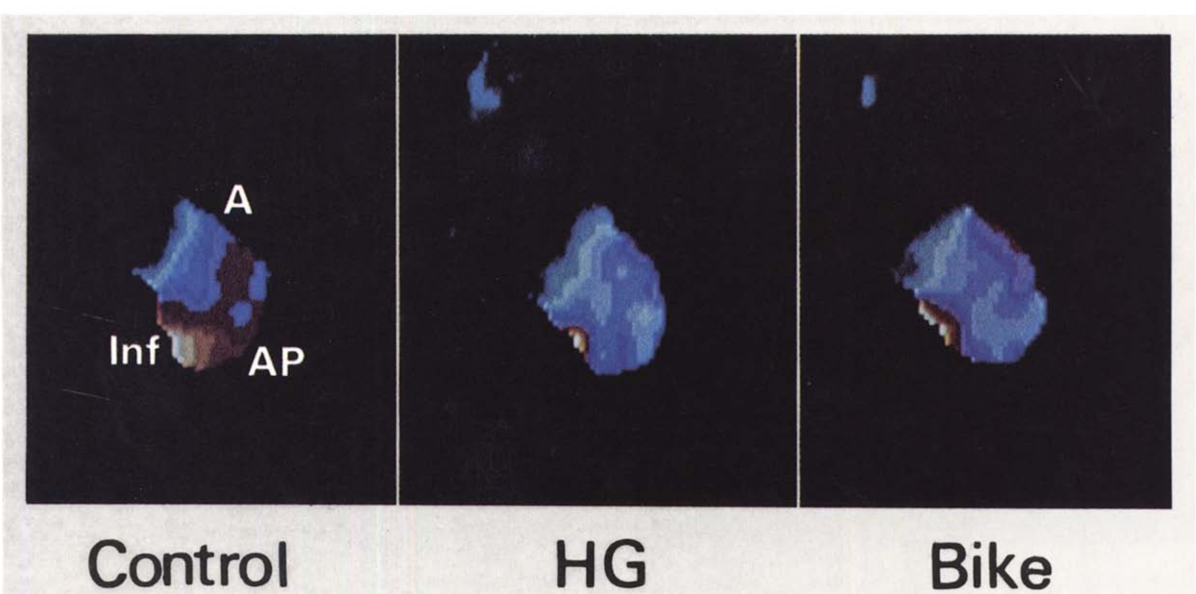

Figure 1. At rest, this patient had an ejection fraction of 66% with a homogeneous contribution from the anterior (A), apical (AP) and inferior zones (Inf). Both handgrip and bicycle exercise resulted in similar decreases in regional ejection fraction involving the anterior and apical zones. Global ejection fraction decreased to 39% during bicycle exercise and to 44% during handgrip exercise. Regional counts are distributed according to a 16 color code, each comprising 6.25% and normalized in both this figure and Figure 2 to the portion of the left ventricle contributing the most to ejection fraction. Black represents the lowest with green, blue and maroon intermediate and red, yellow and white representing the greatest contribution to ejection fraction.

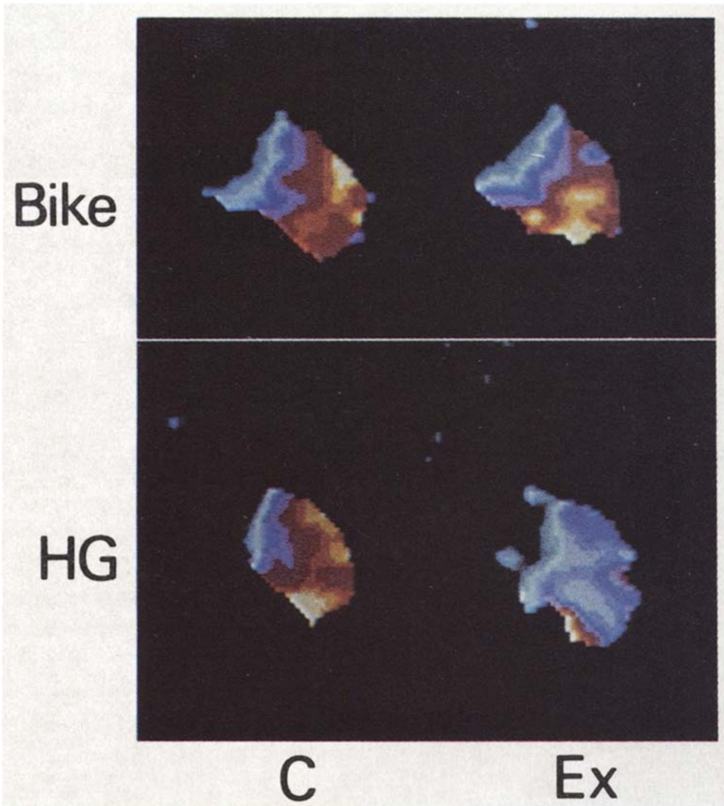

Figure 2. This patient had normal coronary arteries and normal left ventricular contraction during cardiac catheterization. The control (C) study showed a normal regional ejection fraction at rest before both studies Regional ejection fraction remained normal at a rate-pressure product of 33,350 beats·mm Hg per min during bicycle exercise In contrast, during handgrip exercise (HG), with a rate-pressure product of 21,160 beats·mm Hg per min, there was a marked decrease in regional ejection fraction in both the anterior and apical zones (ex = exercise).

sults in a greater stress as evidenced by the almost twofold greater increase in the rate-pressure product primarily due to the sharply greater increases in heart rate. This form of exercise more closely simulates the type of activity usually associated with anginal episodes, providing additional clinically useful data. Thus, there is a balance between technical factors that are more optimal during isometric exercise and the level of stress that is more optimal during isotonic exercise. It is of interest that although some preliminary studies showed that isometric handgrip and bicycle exercise appear equivalent from the standpoint of diagnosis, others showed bicycle exercise to be superior (11). However, significant differences in apparent methodology and end points used for diagnosis limit comparisons and make any conclusions difficult.

Limitations of global ejection fraction. Changes in global ejection fraction during isometric exercise were of little diagnostic value as previously reported (Table 3) (15). With bicycle exercise, changes in global ejection fraction had a sensitivity of 82%. Jones et al. (7) also reported a sensitivity of 81% in patients with a rest ejection fraction of 50% or more. However, in the present study, an absolute change in ejection fraction was associated with a relatively poor specificity of 30%, compared with 60% in that of Jones et al. The poor discriminatory value of changes in global ejection fraction was most apparent in patients with a baseline value of 70% or more. Further analysis provides some insight into this finding: of the 20 patients with normal coronary arteries, 10 had a rest ejection fraction of 70% or more. Gibbons et al. (16) also found that in 11 of 15 patients with an ejection fraction of more than 70%, ejection fraction failed to increase by 5% (5 units) or more.

Although our findings appear to differ significantly from

Table 5. Relative Regional Ejection During Exercise

	Sensitivity	Specificity	PV+	PV−
Handgrip	0.68	0.50	0.66	0.53
Bicycle	0.75	0.65	0 75	0.65
ST segment	0.54	0.90	0 88	0.50

PV+ = predictive value of a positive, PV− = predictive value of a negative

Table 6. Relation Between Bicycle Exercise-Induced Changes in ST Segment and Relative Regional Ejection Fraction (REF)

	Coronary Disease REF		No Disease REF	
	Neg	Pos.	Neg	Pos.
ST segment				
Neg.	5	8	11	7
Pos	2	13	2	0

Neg = negative; Pos = positive

those reported by Borer at al. (3), their study appears to comprise relatively sicker patients, as reflected by the lower average ejection fraction of 49%. Similarly of their normal patients, the vast majority had a rest ejection fraction of less than 70% in contrast to half of our group of patients without coronary disease. Prior studies showed that at rest, left ventricular ejection fraction is similar, whether determined using first pass or gated equilibrium techniques (17), and appears relatively independent of view selection (18). However, further studies are required to compare these two techniques during exercise in view of the disparate results.

Role of segmental wall motion analysis. Experimental studies have shown that segmental myocardial function is a sensitive marker of decreases in myocardial blood flow at rest (14). In addition, exercise can induce regional abnormalities of contraction by causing changes in the supply-demand relation (19). Clinically, the marked inhomogeneity in severity of obstructive coronary disease with varying degrees of reduction in blood flow and resulting ischemic dysfunction makes segmental analysis a logical approach. We (18) previously reported that radionuclide angiography accurately delineates segmental asynergy. Others (20) similarly found a good correlation between quantitative assessment of radionuclide determined regional wall motion and contrast ventriculography. The present study using quantitative wall motion analysis suggests that from the standpoint of sensitivity of disease, handgrip and bicycle exercise are similar; however, owing to a lower specificity, isotonic exercise is superior overall. Similarly, the predictive value of a positive test was 75% with bicycle exercise and 66% with handgrip exercise. Thus, abnormalities in segmental wall motion appear to be independent of baseline ejection fraction.

False positive response. The mechanism responsible for the relatively high rate of false positive responses using handgrip exercise is unclear. Sarnoff et al. (21) in an isolated heart preparation experimentally showed that abrupt increases in afterload were associated with improved left ventricular function and termed this response homeometric autoregulation. However, later studies by Wilcken at al. (22) in the intact dog demonstrated that with an abrupt increase in afterload, left ventricular function showed deterioration lasting approximately 30 seconds. However, studies using handgrip exercise in normal patients did not show deterioration when measurements were made 3 to 4 minutes after initiation of exercise, and fail to support this explanation (23,24).

With regard to patients showing a false positive response to bicycle exercise, Gibbons et al. (16) did find a relation between indexes of left ventricular function at rest and the response to exercise. However, this was of limited value in predicting the likelihood of a false positive response before the performance of the radionuclide study. Similarly, a study from our laboratory (25) identified patient size as the only factor with a greater likelihood of a false positive response.

An alternative explanation is that the abnormal response to exercise is indicative of underlying disease. Cardiac catheterization is performed under conditions of rest and exercise is rarely used. Thus, it is conceivable that subtle abnormalities of left ventricular function not seen at rest may only manifest themselves during exercise. A difficulty with this interpretation is the excellent long-term prognosis of patients with a chest pain syndrome who were found to have normal coronary arteries on cardiac catheterization (26). Furthermore, of the 10 patients with normal coronary arteries and an abnormal response to handgrip exercise, only 4 had an abnormal response to bicycle exercise. This lack of concordance of a false positive response as well as the excellent prognosis make this a difficult explanation to support.

Clinical implications. The present study shows that in patients without evidence of significant left ventricular dysfunction at rest, as defined by the absence of pathologic Q waves and a rest ejection fraction of 50% or more, upright bicycle exercise combined with radionuclide angiography and analysis of regional ejection fraction provide the optimal combination of sensitivity and specificity. It is to be expected that with further refinement of technology these results will improve. In particular, introduction of new imaging agents with a short half-life will allow multiple injections permitting studies in different projections, thereby providing a more complete examination of the heart. In addition, early data on technetium-based perfusion agents suggest that simultaneous analysis of regional wall motion and perfusion may be close at hand (27,28).

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