The Frequency of Asymptomatic and Electrically Silent Exercise-Induced Regional Myocardial Ischemia During First-Pass Radionuclide Angiography with Upright Bicycle Ergometry

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The presence of asymptomatic (silent) myocardial ischemia during provocative testing may limit the detection of ischemic heart disease, unless sensitive indicators of ischemia are utilized. Exercise ventricular function studies are well suited for ischemia detection since segmental dysfunction is an early pathophysiologic event in the ischemic cascade. In this study, we examined the rest and stress first-pass radionuclide angiographic studies of 104 patients with coronary artery disease and exercise-induced regional wall motion abnormalities. Asymptomatic ischemia was observed in 83 patients, while only 21 patients were symptomatic. Clinical variables were not different between the two groups, except for a higher frequency of a prior anginal history in the symptomatic group. The peak heart rate and pressure-rate product were significantly higher in the silent ischemia group, as these patients are not limited by symptoms. Wall motion scores, resting and exercise ejection fractions were similar in the two groups. The frequency of an ischemic electrocardiographic ST-segment response was low, and was not significantly different between groups. These data indicate that electrically and symptomatically silent myocardial ischemia are frequent occurrences with upright bicycle ergometry. Without adjunctive cardiac imaging, this mode of exercise may not be appropriate for the evaluation of ischemic heart disease.

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The prognosis of patients with asymptomatic myocardial ischemia detected on exercise testing or by ambulatory ECG monitoring may actually be worse than the prognosis of patients who have overt clinical manifestations of myocardial ischemia (*1–4*). Differences between silent and painful myocardial ischemia may lie in the origination, conduction and perception of pain (*5,6*).

With metabolic imaging, it has been demonstrated that some patients with silent ischemia on treadmill exercise have at least as great an extent of ischemic myocardium as patients with painful exertional ischemia (*7*). However, the severity or duration of ischemia may be an important factor in the development of symptoms in patients with a high nociceptive threshold (*8,9*). Thus, silent ischemia may be provoked more frequently in exercise protocols in which the duration and effort of stress is less, as in bicycle ergometric exercise testing.

The principal aim of this study was to determine the frequency of asymptomatic myocardial ischemia during upright bicycle exercise performed with first-pass radionuclide angiography (RNA) in a group of patients with angiographically defined coronary artery disease in whom regional wall motion worsened with exercise. We examined this group of patients for clinical variables which might be associated with the presence of silent bicycle ergometry induced ischemia. Lastly, we compared the relative frequency of asymptomatic ischemia, electrically silent ischemia, and an abnormal exercise ejection fraction response during exercise in these patients.

METHODS

Patient Population

We retrospectively examined 104 rest and exercise RNA studies of patients who met the following criteria: (1) angiographically defined coronary artery disease and (2) RNA evidence for exercise-induced worsening of segmental wall motion in the usual regional distribution of the angiographic coronary artery disease. These criteria were utilized in order to ensure the selection of only those patients with true-positive regional ischemic abnormalities.

All patients underwent rest and upright bicycle exercise first-pass RNA, which was limited by symptoms or attaining at least 85% of predicted maximal heart rate. Rest and exercise ejection fraction, regional wall motion, and ST-segment response on the electrocardiogram were measured during RNA testing, and the development of cardiac symptoms during exercise or recovery was recorded. Patients were also categorized by age, gender, their history of cardiac symptoms at rest or activity, previous coronary artery bypass graft surgery, prior myocardial infarction, and history of diabetes mellitus.

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Rest and Exercise RNA Imaging

RNA was performed by the first-pass technique with a multicrystal gamma camera and computer (Baird System-77) fitted with a 1-inch parallel-hole collimator, or a single crystal high count rate gamma camera fitted with a high-sensitivity parallel-hole collimator (Elscint Apex 409-AG, Hackensack, NJ). Images were obtained with the patient seated upright in the anterior projection.

After resting blood pressure measurement, a 15–20-mCi bolus injection of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) in a volume of less than 1 ml was given by rapid flushing with 30 ml of normal saline through a large bore (14- or 16-gauge) indwelling catheter in an antecubital or external jugular vein.

Exercise was performed on an isokinetic bicycle ergometer (Fitron, MA) beginning at 200 kilopond-meters per minute and increasing 100 kilopond-meters/minute until leg exhaustion (quadriceps muscle) or cardiac symptoms (chest discomfort or dyspnea) occurred. Continuous 12-lead ECG monitoring with computer averaging (Marquette Electronics, Milwaukee, WI) was performed. Blood pressures were obtained every 2 min throughout exercise and at peak exercise. At peak exercise, the first-pass RNA was repeated. Images were acquired in frame mode for 30–40 sec using 40 to 50 msec frames at rest, depending on the heart rate, and a frame time of 20 to 25 msec was utilized during exercise.

Prior to exercise imaging, background counts in the cardiac region were acquired for 3 sec. A second bolus of 20–25 mCi of ^{99m}Tc-DTPA was injected at peak exercise, while the patient continued to pedal. The patient's chest was stabilized against the collimator during exercise acquisition to improve image quality by preventing excessive chest wall motion.

Data Analysis

The cardiac history of each patient was obtained prior to exercise. During the exercise study each patient was interrogated for the development of chest discomfort, dyspnea or any presenting anginal equivalent. After exercise, each patient was again asked to describe any symptoms occurring during the study, as well as the reason for exercise termination.

The exercise ECG was interpreted as positive for myocardial ischemia if the exercise tracing developed 1 mm of horizontal or downsloping, or 1.5 mm of upsloping, ST-segment depression 80 msec after the J-point. The tracing was considered uninterpretable if the resting ECG showed marked resting ST-segment abnormalities, left ventricular hypertrophy with a strain pattern, left bundle branch block, or if ST-segment abnormalities occurred in a patient taking digitalis.

RNA studies were analyzed using the commercially available computer software of Baird-Atomic and Elscint systems. The resting and exercise heart rate, blood pressure and ejection fraction were tabulated for each test. Regional wall motion was scored using the following scale: 0 = normal, 1 = mild hypokinesis, 2 = moderate hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. The anterior projection RNA image was divided into five segments. The anteroseptal segment grades were inferred from regional ejection fraction functional image. The apical, anterolateral, inferior and inferobasal segments were analyzed by cine loop as well as regional ejection fraction images (Figs. 1 and 2). An increase of less than five ejection fraction points defined an abnormal response to exercise.

Coronary angiographic data were correlated with the segmental wall motion response to exercise. An arterial stenosis of greater than 50% was considered significant. Each stenosis was scored on a scale of 1 to 5, where 1 = 50% stenosis or less, 2 = 50% to 70%, 3 = 70% to 90%, 4 = 90% to 99%, and 5 = 100% (total occlusion). Overall coronary disease scores were the sum of these arterial scores for each patient. For the definition of true-positive wall motion abnormalities, the anteroseptal and apical segments were considered to be in the distribution of the left anterior descending coronary artery. The inferobasal, inferior, and apical (inferior portion) segments were assumed to be in the distribution of the posterior descending (either right coronary or circumflex artery, depending on arterial dominance). The anterolateral and apical (lateral portion) segments were considered to be in the diagonal (left anterior descending) or obtuse marginal (circumflex) artery distribution.

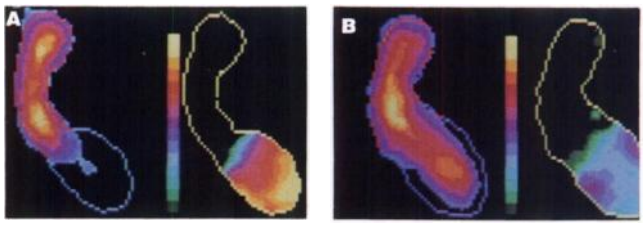

FIGURE 1. First-pass RNA images obtained in a 72-yr-old man with a history of typical angina pectoris are shown. The resting left ventricular end-diastolic perimeter and end-systolic counts (A, left image) demonstrate normal ventricular size and wall excursion. Regional systolic performance is also assessed with a regional ejection fraction image (A, right image), which shows a normal regional ejection fraction pattern (A, right) at rest. The resting ejection fraction was 76%. With exercise to a heart rate of 126 bpm, he developed typical angina pectoris and ST-segment depression on ECG. Stress RNA demonstrated slightly left ventricular dilatation with a marked fall in ejection fraction to 38% (B, left). The regional ejection fraction pattern shows anteroseptal moderate hypokinesis with apical severe hypokinesis and tardokinesis (B, right). Coronary angiography revealed a tight proximal left anterior descending coronary artery stenosis.

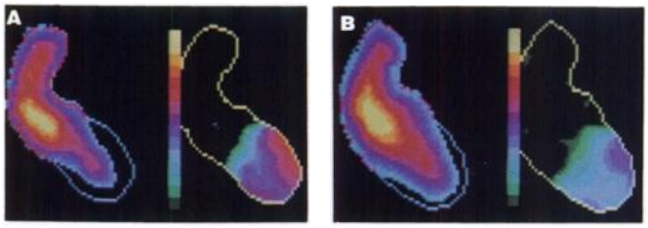

FIGURE 2. First-pass RNA images on a 64-yr-old woman with multiple risk factors for coronary artery disease, but no anginal symptoms demonstrate upper-normal left ventricular size (A, left image) and low-normal systolic performance (ejection fraction 53%). The regional ejection fraction image (A, right) demonstrates mild anteroseptal, apical and inferoapical hypokinesis. With exercise up to a heart rate of 154 bpm, she developed leg fatigue without cardiac symptoms. No ST-segment depression occurred on ECG. The exercise study demonstrated marked left ventricular dilatation with a fall in left ventricular ejection fraction to 37% (B, left). The regional ejection fraction pattern shows inferior mild hypokinesis, anteroseptal and inferobasal moderate hypokinesis, with apical severe hypokinesis (B, right). Coronary angiography revealed tight stenoses in the proximal left anterior descending and mid-right coronary arteries.

Statistical Analysis

For continuous variables, the mean values of each group were compared using the unpaired t-test (comparison of means). These data are presented as mean and standard deviation. Chi-square analysis with one degree of freedom was applied to the frequency of clinical characteristics and ratios of binary exercise test variables. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Utilizing an inclusive definition of cardiac symptomatology, there were 21 symptomatic and 83 asymptomatic cases out of the 104 patients with evidence for exercise induced regional myocardial ischemia. These 21 symptomatic cases included 13 patients with typical angina pectoris, i.e. retrosternal chest discomfort with exercise which was relieved by rest and/or nitroglycerin (Fig. 1). There were five patients who developed neck, throat or arm discomfort, and three patients who complained of severe dyspnea (an anginal equivalent). The 83 patients with silent ischemia stopped exercise because of excessive leg fatigue (predominantly quadriceps femoris muscle), with or without mild dyspnea which they felt to be appropriate for their level of exertion, or were stopped by the physician after having exceeded target heart rate (Fig. 2). These results are summarized in Table 1.

Clinical Characteristics

The silent ischemia group was comprised of 54 men and 29 women (65% male) with a mean age of 60 ± 13 yr. The symptomatic group had 14 men and seven women (67% male) with a mean age of 60 ± 10 years. These variables were not statistically different.

There were 59 patients out of the 104 with a pre-test history of cardiac symptoms, including exertional chest, arm or neck discomfort, exertional dyspnea, nonexertional chest pain, or recent symptomatic myocardial infarction. Only 21 of these 59 developed symptoms during the exercise study. However, none of the 45 patients without symptoms developed symptoms during RNA ($p < 0.001$). Thus, the frequency of cardiac symptoms prior to exercise testing was 100% (21 of 21) in the symptomatic group, but only 46% (38 of 83) in the silent ischemia group ($p < 0.001$).

The frequency of diabetes mellitus was only 5% in the symptomatic group (1 of 21), and 16% in the silent ischemia group (13 of 83). Of the 21 symptomatic patients, five (24%) had undergone coronary artery bypass grafting prior to the test, as had 21 of the 83 silent ischemia patients (25%). Evidence for previous infarction was identified in 12 symptomatic patients (57%) and in 49 of the silent ischemia patients (59%). None of these minor differences were statistically significant. The incidence of silent ischemia among patients with diabetes (93%), bypass surgery (79%), or prior myocardial infarction (80%) was not significantly different from the proportion of silent ischemia in patients without these variables (78%, 79%, and 81%, respectively). Similarly, the 26 patients with none of these variables had no greater frequency of silent ischemia than those patients with one or more of these clinical factors (23% versus 19%, p = ns).

Exercise, Angiographic and RNA Variables

As the patients in the silent ischemia group did not terminate exercise due to cardiac symptoms, their peak

TABLE 1
Exercise-Induced Ischemia: Clinical, Exercise and Radionuclide Angiographic Variables with Silent or Symptomatic Exercise-Induced Myocardial Ischemia

Characteristic or variable	Silent	Symptomatic	P value
Number of patients	83	21	NS
Males (%)	65	67	NS
Age (yr)	60 ± 13	60 ± 10	NS
Angiographic CAD score	16.4 ± 9.1	16.4 ± 8.0	NS
History of:			NS
Angina or equivalent	46%	100%	$p < 0.001$
Diabetes mellitus	16%	5%	NS
Myocardial infarction	59%	57%	NS
Coronary bypass surgery	25%	24%	NS
Exercise Variables:			NS
Peak heart rate (bpm)	138 ± 20	125 ± 24	$p < 0.02$
Peak-double product (×1000)	26.0 ± 5.3	22.5 ± 7.0	$p < 0.05$
ECG positive and interpretable	20/65 (31%)	8/17 (47%)	NS
RNA Variables:			NS
Resting ejection fraction	48.3% ± 14.5%	48.9% ± 12.0%	NS
Exercise ejection fraction	40.0% ± 10.7%	40.5% ± 10.3%	NS
Change in ejection fraction	−8.3% ± 9.2%	−8.5% ± 9.1%	NS
Resting wall motion score	3.5 ± 4.0	3.0 ± 3.6	NS
Exercise wall motion score	7.7 ± 3.8	7.5 ± 3.3	NS
Change in wall motion score	4.4 ± 3.3	4.5 ± 2.7	NS

exercise heart rate and peak double product were higher than those of the symptomatic group (138 ± 20 bpm versus 125 ± 24 bpm, $p < 0.02$; and 25,996 ± 5, 286 mm Hg-bpm versus 22,537 ± 6,998 mm Hg-bpm, $p < 0.05$).

The ECG was interpretable for ischemia in 17 of the 21 symptomatic patients, and in 65 of the 83 silent ischemia patients. Of the 17 ECGs in the symptomatic group, eight were positive for myocardial ischemia, while 20 of the 65 were positive in the silent group (47% versus 31%, p = ns).

The severity of coronary artery disease on angiography, as estimated by the sum of the stenosis scores, was not significantly different between the two groups (16.4 ± 8.0 for symptomatic and 16.4 ± 9.1 for silent ischemia).

Mean regional wall motion scores at rest (3.0 ± 3.6 for symptomatic and 3.5 ± 4.0 for silent ischemia), at exercise (7.5 ± 3.3 for symptomatic and 7.7 ± 3.8 for silent ischemia), and the mean worsening from rest to stress (4.5 ± 2.7 for symptomatic patients and 4.4 ± 3.3 for silent ischemia) were not significantly different.

Similarly, there was no difference in the resting ejection fraction (48.3% ± 14.5% for silent ischemia versus 48.9% ± 12.0% for symptomatic), stress ejection fraction (40.0% ± 10.7% for silent ischemia versus 40.5% ± 10.3% for symptomatic), or the mean fall in ejection fraction with exercise (−8.5 ± 9.1 for symptomatic and −8.3 ± 9.2 for silent ischemia). The frequency of an abnormal ejection fraction response (i.e., a less than 5 point rise in ejection fraction) was high in both groups (100% of symptomatic and 89% of silent ischemia, p = ns).

In this population of patients selected for regional wall motion deterioration during exercise, the ejection fraction response to exercise was the test parameter most likely to reflect the ischemia. The ejection fraction response was abnormal in 91%, while an abnormal exercise ECG was present in 34%, and the development of angina occurred in only 20% ($p < 0.001$ for both ejection fraction response versus ECG response and angina; $p < 0.05$ for ECG versus angina).

DISCUSSION

Silent Ischemia: Detection and "Risk Factors"

Most, if not all, patients with ischemic heart disease experience episodes of asymptomatic ischemia. In recent years, many noninvasive diagnostic techniques have enabled the detection of episodes of myocardial ischemia that otherwise would have been unapparent. Exercise testing and Holter monitoring have been used frequently for this purpose (*2,4*). However, myocardial perfusion and ventricular function studies are even better suited for ischemia detection than the ECG, since perfusion disparities and segmental dysfunction are pathophysiologically earlier events in the ischemic cascade (*10,11*). These concepts are underscored by the findings of this study. Despite the presence of significant coronary stenoses and exercise induced ischemic wall motion abnormalities, relatively few (27%) of our patients had both an interpretable ECG and ECG evidence for their ischemia. Even fewer patients (20%) had cardiac symptoms during the study.

Previous studies have suggested that the presence of diabetes mellitus, bypass surgery, or prior myocardial infarction may predispose patients to have silent rather than symptomatic myocardial ischemia. Silent ischemia is certainly a common finding in diabetics with coronary artery disease, with or without concommitant diabetic neuropathy (*12,13*). Symptomatic patients may become asymptomatic after coronary artery bypass surgery, despite the persistence of myocardial ischemia (*14*). Janosi et al. (*15*) found that among patients with ECG evidence for exercise-induced myocardial ischemia, 40% had painless ischemia; prior infarction was more frequent in this group than in those with symptomatic ischemia. However, the results of this study are similar to that of Lindsey et al. (*16*), in which none of these clinical factors was more prevalent in the group of patients with silent ischemia. This may, in part, have been due to the low frequency of diabetes and bypass surgery in our study population (13% and 25%, respectively).

Clinical Importance of First-Pass RNA

Rest and exercise RNA is a powerful prognostic tool in patients with known coronary artery disease. The decision to perform invasive angiographic evaluation or myocardial revascularization can be guided by its results (*17–19*). This noninvasive approach has been found to have a similar amount of prognostic information as can be obtained with coronary angiography (*19*). In recent years, this technique has been relegated to a less important diagnostic role in comparison with ^{201}Tl scintigraphy, partly due to its perceived poor specificity (*20*). Further, in comparison with gated equilibrium RNA ("MUGA"), first-pass RNA has been less widely performed. It is more technically demanding and requires high count rate capability which has not been available in most nuclear laboratories.

However, the recently developed ^{99m}Tc-labeled myocardial perfusion agents, such as ^{99m}Tc-sestamibi, promise to make first-pass RNA a more widely utilized technique (*21*). With ^{99m}Tc-labeled tracers, it will be possible to examine simultaneously right and left ventricular global and regional systolic performance, along with myocardial perfusion both at rest and exercise. This should increase the diagnostic and prognostic information obtained with exercise testing in those medical centers with first-pass expertise (*22*). Since the treadmill exercise test has become the standard adjunct for myocardial perfusion imaging with ^{201}Tl, treadmill exercise first-pass imaging is currently under development, along with the correction algorithms for patient motion. Until this method becomes widely available, a combined perfusion/function study will most likely be performed with bicycle exercise testing.

The findings of our study suggest that the identification of exercise-induced ischemia should be performed with heavy reliance on the more sensitive scintigraphic vari-

ables, with relatively less emphasis upon the development of exercise-induced cardiac symptoms or ECG abnormalities.

Study Limitations

Since global ejection fraction is essentially summed regional performance, the selection of patients with definite regional ischemia biases the study to demonstrate a larger frequency of abnormal ejection fraction responses. Similarly, occasional patients may manifest ECG evidence for exercise-induced ischemia in the absence of regional wall motion abnormality. Although some of these patients have "false-positive" ECGs, a low-resolution nuclear wall motion technique will not detect abnormality in all ischemic patients. Therefore, the conclusions of this study may not uniformly apply to the evaluation of all patients with coronary artery disease. However, in those patients with ischemic regional abnormality severe enough to be detected by first pass, many will not have symptomatic or ECG evidence for ischemia, and would be missed without the imaging modality.

Technically, despite the use of functional images with first-pass imaging, the vascular supply of a given regional wall motion abnormality may be difficult to ascertain. The functional regional ejection fraction image provides information about segments not seen on edge in the anterior projection, but the anteroseptal and posterior walls are overlapped. Investigators have recognized a "circumflex pattern" of diffuse basal abnormality in regional ejection fraction which results from posterior ischemia being imaged in the anterior projection (*23*). However, this pattern can be difficult to distinguish from global myocardial ischemia. More importantly, each patient served as their own control, comparing rest and exercise images; only patients with definite evidence of worsening wall motion with exercise are included. Recent evidence suggests that the location of ischemia does not influence the development of concommitant symptoms (*6*). Thus, potential misassignment of an arterial supply does not mitigate the conclusions of this study.

This study does not allow direct inferences to be made about the incidence of silent exercise induced ischemic abnormalities with other exercise testing modalities or positions. Both supine bicycle and upright treadmill exercise testing have been associated with a greater degree of ST-segment abnormalities, at a given heart rate, than upright bicycle exercise (*24–26*). Similarly, scintigraphic evidence for ischemia may be more intense with supine exercise than with upright (*27*). It should be noted, however, that relatively small differences in the overall frequency of ischemic responses between these techniques have been reported. No direct comparison of treadmill and upright bicycle is currently available, but important disparities between the frequency of symptoms, ECG and imaging evidence for ischemia could be expected with other exercise protocols.

CONCLUSIONS

Asymptomatic and electrically silent myocardial ischemia are very frequent occurrences during symptom-limited upright bicycle testing in patients with scintigraphic wall motion evidence for exercise-induced myocardial ischemia. Cardiac symptoms are very unlikely to occur in patients who do not present with a recognizable angina pectoris or anginal equivalent pattern. However, patients with known symptoms also have a high frequency of silent ischemia during this type of exercise study.

Relative to regional wall motion, the development of angina during upright bicycle exercise is infrequent (20%) and is improved upon only slightly by the exercise ECG (34%, when interpretable). Expectantly, the exercise ejection fraction response has much higher frequency of abnormality (91%) in patients with exercise-induced regional contractile deterioration.

No clinical, ECG or ventricular function parameters were markers for an increased likelihood of developing silent ischemia. The scintigraphic ischemic burden and angiographic extent of disease were similar in patients with symptomatic and asymptomatic ischemia.

The findings of this study may result from the shorter exercise duration and lower peak heart rate attained with bicycle exercise in comparison with treadmill exercise (*26*), resulting in an inherently shorter duration of ischemia and less metabolic sequelae. Moreover, these data suggest that upright bicycle exercise ergometry stress should not be used without adjunctive cardiac imaging for the diagnosis or complete evaluation of patients with previously documented coronary stenoses, or patients with a high likelihood of ischemic disease.

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