Effects of Maximal Exercise Stress on Left Ventricular Function in Patients with Coronary Artery Disease Using First Pass Radionuclide Angiocardiography

A Rapid, Noninvasive Technique for Determining Ejection Fraction and Segmental Wall Motion

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SUMMARY Angiographically determined changes in segmental wall motion (SWM) and ejection fraction (EF) are sensitive indices of left ventricular (LV) function. To compare the effects of exercise on LV function, first pass radionuclide angiocardiography was used before and during maximal upright bicycle stress in patients with nonsignificantly stenosed coronary arteries, and in those with > 75% stenosis. Gamma camera acquisitions were made in the 30° RAO projection using a 20 mCi I.V. bolus of 99mTc-pertechnetate. In the control group (seven normals, one nonsignificant CAD) the EF significantly increased between rest and exercise (0.65 ± 0.03 to 0.81 ± 0.03 (mean ± SEM), p < 0.005). In this group SWM measured over the two anterior and two inferoposterior segments uniformly increased. In the 11 patients with a history of angina and significant coronary artery obstruction, the EF did not change in three and significantly decreased in the remaining eight (0.57 ± 0.04 to 0.45 ± 0.03, p < 0.005). In all 11 patients SWM either decreased or did not increase in the areas supplied by the significantly stenosed coronary arteries. Upright maximal stress angiocardiography appears to be well-suited for diagnosing ischemic heart disease and localizing the area of ischemic dysfunction.

ANGIOGRAPHICALLY DEMONSTRABLE severe coronary artery disease is not always associated with myocardial ischemia. Areas of myocardium formerly supplied by a now totally occluded artery can have adequate blood supply from collateral vessels. The physiological significance of a coronary artery obstruction can be obtained by assessing its effects on left ventricular function. However, because of myocardial oxygen supply-demand relationships, left ventricular function may be normal under resting conditions when metabolic demands are low, even in the presence of high grade coronary artery obstruction.

Stress electrocardiography is based on this fundamental principle. However, a number of false positive and false negative results occur with this technique.

The accepted standard method for evaluating the functional significance of coronary artery obstruction is the measurement of left ventricular segmental contraction using the left ventriculogram obtained during cardiac catheterization. This procedure involves some degree of discomfort and risk to the patient, as well as considerable expense. Further, exercise stress-induced changes in left ventricular function are not usually evaluated.

Electrocardiography and systolic time intervals permit only indirect evaluation of left ventricular function during exercise. Echocardiography allows the direct evaluation of left ventricular function at rest. Radiotopic techniques permit the evaluation of left ventricular function, i.e., ejection fraction and regional wall motion, at rest or with supine exercise, but have not been applied to studying the patient during maximal upright exercise stress.

The purpose of this study was to develop a noninvasive, rapid and easily repeatable radionuclide technique for the determination of left ventricular ejection fraction and segmental wall motion both at rest and during maximal upright exercise stress.

Materials and Methods

Patient Selection

Thirty-eight first pass radionuclide angiocardiograms were performed in 19 patients. The control group consisted of eight patients. Four had no signs, symptoms or electrocardiographic evidence of coronary artery disease either at rest or during exercise stress. Of the other four, three had normal coronary arteries and one had < 50% coronary artery obstruction. The ages ranged from 24-63 years (mean age 47 years)
The coronary artery disease group consisted of 11 patients. Ten had a classical history of angina; one was asymptomatic but had a strong family history of early heart disease. Coronary arteriography demonstrated > 75% occlusion of at least one vessel (table 1). The ages ranged from 42–64 years (mean 56 years). All studies were performed at least 48 hours after cessation of propranolol therapy and at least 4 hours after a nitroglycerin dosage.

### First Pass Technique

Each patient was studied at rest using 99mTc technetium-DTPA, and the study was repeated 4–24 hours later during exercise. All patients were in the fasting state.

A 20-second list mode acquisition was made directly onto the disc of a minicomputer after a 20 mCi bolus of technetium-99m pertechnetate was flushed into the antecubital vein. The exercise was continued while the acquisition was obtained.

The technique of first pass radionuclide angiography has been shown to have little variation in resting ejection fraction determinations when serial assessments are performed over a 1–2 week period.

### Exercise Protocol

Before the start of exercise a #20 gauge Jelco polyethylene catheter was placed into an antecubital vein and connected to a slow infusion of a 5% solution of dextrose in water. Standard electrocardiographic electrodes were then attached so that the 6 limb leads and lead V₅ could be recorded before and during each stage of the exercise protocol.

Exercise was performed using a bicycle ergometer. The starting work load was 75 kpm and was increased at 1-minute intervals in steps of 75 kpm. The end point was either the attainment of maximum predicted heart rate, flat ST segment depression of at least 1 mm, frequent ventricular ectopy, severe chest pain or severe fatigue.

To perform studies at the time of maximum upright exercise stress required overcoming the problem of patient motion relative to the gamma scintillation camera detector. To accomplish this, the exercise was performed with the subject facing the camera detector (mobile Ohio Nuclear Sigma 420, equipped with high resolution collimator) in the 30° RAO projection while seated on the bicycle ergometer. A 30° foam rubber wedge was placed between the patient’s left chest and the detector in order to maintain the 30° RAO projection. The subject was then held to the detector and the wedge by a strap around his back, connected at each of its ends to the camera detector. In addition, the subject grasped the arms of the detector gantry with his arms. The mobile camera detector gantry has a small amount of free movement such that it moves with the patient while he pedals the bicycle. In this way the patient was motionless relative to the detector, since patient motion is transferred to the camera gantry itself.

### Data Processing

After the intravenous bolus injection, the list mode data was simultaneously recorded by the camera's high speed (75 inches/sec) magnetic tape drive and acquired directly onto the disk of a minicomputer system (Informatek Simis 3) for calculation of ejection fraction and determination of segmental wall motion.

The study was first reviewed for motion artifact using the persistence mode of the minicomputer display. Only one study was deemed unacceptable because of motion artifact. Ejection fraction was then calculated from a background — corrected left ventricular time-activity curve framed with a time increment of 40 msec (fig. 1), as previously described. Segmental wall motion analysis was performed by dividing each of four sequential cardiac cycles into 16 frames and adding the respective frames from each of the cycles to yield one composite cycle made up of 16 frames (fig. 2). From these 16 frames a left ventricular volume curve was obtained by plotting the activity from the left ventricular region of interest (fig. 3). From this curve the end-diastolic and end-systolic frames were identified. The outlines of the end-diastolic and end-systolic images were then obtained using a modified second derivative method and superimposed to yield a static representation of segmental wall motion. For evaluation of regional wall motion the left ventricular outline was divided into four segments: anterobasal, anterobasal, inferoapical and inferobasal. Each segment was assessed by three different observers and judged to be either dyskinetic, akinetic, hypokinetic, normal or hyperkinetic. In ad-

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**Table 1. Coronary Artery Disease Group (Resting)**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Site of coronary artery obstruction*</th>
<th>Contrast angiogram</th>
<th>Location of wall motion abnormality</th>
<th>Radionuclide angiogram</th>
<th>Location of wall motion abnormality</th>
</tr>
</thead>
<tbody>
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<td>IA</td>
<td>IA</td>
<td>IA</td>
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</tr>
<tr>
<td>2</td>
<td>RCA, LAD, LCA</td>
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<td>o</td>
<td>o</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LAD</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td></td>
</tr>
<tr>
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<td>RCA, LAD</td>
<td>AB, AA, IA, IB</td>
<td>AB, AA, IA, IB</td>
<td>AB, AA, IA, IB</td>
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</tr>
<tr>
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<td>IA</td>
<td>IA</td>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LAD</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td>7</td>
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<td>o</td>
<td>o</td>
<td>o</td>
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</tr>
<tr>
<td>8</td>
<td>RCA</td>
<td>IA, IB</td>
<td>IA, IB</td>
<td>AA, IB</td>
<td></td>
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<tr>
<td>9</td>
<td>LAD</td>
<td>AB, AA, IA</td>
<td>AB, AA, IA</td>
<td>AA, IA</td>
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</tr>
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<tr>
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<td>LAD</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td></td>
</tr>
</tbody>
</table>

*Greater than 75% obstruction.

Abbreviations: AB = anterobasal; AA = anterobasal; IA = inferoapical; IB = inferobasal; o = no abnormalities; LAD = left anterior descending; LCA = left circumflex; RCA = right circumflex.
diation, the 16 sequential frames of the composite cardiac cycle were repetitively and sequentially displayed on the color television monitor to yield a dynamic, flicker-free representation of wall motion in an interpolated 512 $\times$ 512 matrix.

Comparison First Pass RAO and Gated AO Angiocardiograms

In order to compare the ability to detect regional wall motion abnormalities in the two different projections, the following studies were performed.

![Figure 1](image1.png)

**Figure 1.** Typical left ventricular time (x axis) vs activity (y axis) curve. The peaks of radioactivity correspond to end-diastole (ED) and the lowest points of activity correspond to end-systole (ES). Also shown is the background activity curve which is subtracted from the left ventricular curve to yield the background-corrected left ventricular time activity curve. Ejection fraction (EF) was calculated for each of four successive cardiac cycles, starting with the cycle with the highest activity. These values are then averaged.

![Figure 3](image3.png)

**Figure 3.** Left ventricular volume curve with radioactivity (proportional to blood volume) plotted on the y-axis and time with respect to the 16 frames of the composite image, plotted on the x-axis.

In a separate group of 19 consecutive patients referred for routine radionuclide angiocardiograms, a first pass study was obtained in the RAO projection during an intravenous bolus injection of 25 mCi of $^{99m}$technetium-human serum albumin. After a 15-minute equilibrium period, a computer-gated, 4 million count acquisition was obtained, using a high resolution collimator, in the LAO projection. The computer algorithm consisted of dividing the cardiac cycle length, determined from the preceding R-R intervals, into sixteenths, and accumulating counts into the appropriate registers. Typical acquisition times varied from 4–5 minutes.

Ejection fraction was determined from the background-corrected left ventricular activity curve, and regional wall motion evaluated from an image formed by the superimposition of the systolic and diastolic contours. Group comparisons were made using the t test, and comparisons of two studies in individual patients were made by the paired t test.

**Results**

**Controls**

In the control group of eight patients, the ejection fraction uniformly increased from rest to exercise: 0.65 $\pm$ 0.03 to 0.81 $\pm$ 0.03 (mean $\pm$ SEM), $p < 0.005$ (fig. 4). Segmental wall motion measured over the two anterior and two inferoposterior segments was uniformly increased during exercise in these patients (table 2).

**Coronary Artery Disease Group**

In the 11 patients with a history of angina and/or angiographically significant coronary artery disease the ejection fraction decreased in eight and did not change in three patients: from 0.57 $\pm$ 0.04 to 0.45 $\pm$ 0.03, $p < 0.005$ (fig. 4). Six of the 11 patients (55%) had resting ejection fractions $> 0.55$. One
(patient 3) who had normal wall motion and ejection fraction at rest had complete occlusion of the left anterior descending coronary artery (LAD) but also had extensive collateral vessels supplying the former distribution of the LAD. However, during exercise stress she developed marked contraction abnormalities (fig. 5).

In all 11 patients segmental wall motion either decreased or failed to manifest the normally expected increase in the areas supplied by the stenosed coronary arteries (table 3). In the three patients whose ejection fraction did not change during exercise, there was either an increase or no change in segmental wall motion in the areas supplied by the non-stenosed coronary arteries. Six of the 11 patients who developed stress angiographic abnormalities had chest pain and only four had electrocardiographic changes during maximal exercise stress (table 3).

Comparison of First Pass RAO and Gated LAO Angiograms

The ejection fractions determined in the 19 patients ranged from 0.26-0.81. Their mean values (± SEM) were: 0.48 ± 0.04 for the first pass technique, and 0.51 ± 0.04 for the gated technique (table 4). Correlation was excellent with $r = 0.89$ ($y = 0.87x + 3.43$).

Regional wall motion correlation was also good, in that whenever an anterior or apical defect was seen in the RAO projection, a defect was also seen in an anatomically contiguous area in the LAO projection (table 4). However, in the two patients with inferior wall motion defects in the RAO projection, no regional abnormalities were seen in the LAO projection.

**Discussion**

Angina is caused by an imbalance between myocardial oxygen supply and demand. The severity and frequency of anginal episodes, however, does not correlate with the degree of coronary artery obstruction. There are many reports of patients with relatively severe coronary artery disease without symptoms of angina. The physiological significance of coronary artery obstruction depends upon whether the relationship between myocardial oxygen supply and demand results in ischemia, with subsequent impairment of left ventricular function.

Ejection fraction is a useful clinical indicator of global left ventricular function, but may not reveal small changes in regional contractility. Abnormalities

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**Table 2. Normal Patients**

<table>
<thead>
<tr>
<th>Exercise stress</th>
<th>Heart rate</th>
<th>Chest pain</th>
<th>ST depression</th>
<th>Ejection fraction</th>
<th>Segmental wall motion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>H 150</td>
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<td>-</td>
<td>-</td>
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<td>95</td>
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</tbody>
</table>

**Abbreviations:** + = present; = absent; AB = anterobasal; AA = anteroseptal; IA = inferoseptal; IB = inferobasal; 1+ = dyskinetic; 0 = akinetic; 1+ = hypokinetic; 2+ = normal; 3+ = hyperkinetic.

**Figure 4.** Changes in ejection fraction from rest to exercise in the group of normal patients (left panel) and the group with coronary artery disease (right panel).
in left ventricular segmental wall motion have been shown also to be useful clinical indicators of regional ischemia resulting from stenoses of the coronary arteries supplying the region.\textsuperscript{11-17} When myocardial oxygen demand is increased by exercise stress, regional abnormalities in left ventricular function become manifest in those patients with ischemic heart disease.\textsuperscript{3, 7}

It is not clear whether upright or supine exercise is preferred. We chose the upright position for several reasons. This position probably provides a better laboratory assessment of routine patient activity, since most exercise is accomplished in the upright position.

More important is the effect of hydrostatic pressure on circulatory hemodynamics reflected through the influence of posture on stroke volume. Stroke volume is less in the upright position, but steadily increases with exercise and finally plateaus at a value equal to the resting stroke volume in the supine position. On the other hand, the stroke volume does not change significantly with supine exercise until moderate levels are reached, at which time the stroke volume actually decreases.\textsuperscript{18}

Using the noninvasive technique of first pass radionuclide angiocardiography, we have demonstrated both increases in the extent of regional contraction and ejection fraction during maximal exercise stress in subjects with less than 50\% obstruction to a coronary artery lumen.

However, in those patients with greater than 75\% obstruction of at least one coronary artery, both regional and global abnormalities in left ventricular function became apparent during exercise stress (fig. 5). In three patients with significant coronary artery disease there was no change in global left ventricular function (ejection fraction), but in each there was either a decrease or the absence of the normal increase in segmental wall motion in the areas supplied by the stenosed coronary arteries, confirming the importance of evaluating regional as well as global left ventricular function during stress.

The ejection fraction at rest was not significantly different between those patients with normal and significantly stenosed coronary arteries; this confirms the findings of earlier studies.\textsuperscript{3, 7}

In six of the 11 patients with significant coronary artery disease, chest pain developed during maximal stress, but only four developed ischemic electrocardiographic changes. However, all 11 patients demonstrated an abnormal response in ejection fraction and impairment of segmental wall motion.

First pass radionuclide angiocardiography permits studies to be performed in the RAO projection. This is

<table>
<thead>
<tr>
<th>Table 3. Coronary Artery Disease Patients</th>
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<table>
<thead>
<tr>
<th>Exercise stress</th>
<th>Ejection fraction</th>
<th>Segmental wall motion</th>
</tr>
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<tbody>
<tr>
<td>Pt</td>
<td>Heart rate</td>
<td>Chest pain</td>
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<td>----</td>
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</tr>
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<tr>
<td>11</td>
<td>152</td>
<td>+</td>
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Abbreviations: + = present; - = absent; AB = anterobasal; AA = anteropapical; IA = inferoapical; IB = inferobasal; 1= = dyskinetic; 0 = akinetic; 1+ = hypokinetic; 2+ = normal; 3+ = hyperkinetic.
the preferred projection for single plane contrast angiography. This projection is commonly preferred\textsuperscript{19,20} because it allows visualization of the cardiac apex, anterior and inferior walls (these walls are suboptimally visualized in the LAO projection). The technique is rapid, requiring only 20 seconds of acquisition time, without any prior preparation of the patient.\textsuperscript{21}

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### References

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