Variation in the Size of Jeopardized Myocardium in Patients with Isolated Left Anterior Descending Coronary Artery Disease

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SUMMARY Previous studies show considerable variation in the perfusion and function of the left ventricle at rest and during stress in patients with disease of the isolated left anterior descending coronary artery. In search of mechanisms, we obtained exercise thallium-201 images in 35 such patients. None of the patients had had infarction. The exercise-induced perfusion defect size was measured as the average of the percentage of abnormal perimeter from the three standard projections. The perfusion defect size was smaller in the nine patients with 50–69% stenosis than in the 26 patients with $\geq 70\%$ stenosis (10 ± 9% vs 27 ± 15%, mean ± sd, $p < 0.01$). Among the 26 patients with $\geq 70\%$ stenosis, the perfusion defect was $\leq 30\%$ in 14 and $> 30\%$ in 12. All 14 patients with perfusion defects $\leq 30\%$ were older than 50 years; eight of the 12 with perfusion defects $> 30\%$ were 50 years or younger ($p = 0.0003$). The severity and site of stenosis, collaterals, exercise heart rate and double product, propranolol therapy and results of exercise ECG were similar in patients with perfusion defects $\leq 30\%$ and in patients with perfusion defects $> 30\%$. Using a stepwise regression analysis of 30 clinical, anatomic and exercise variables, only age showed a significant correlation with perfusion defect size ($r = -0.58$, $p < 0.005$). In patients with effective collaterals, the perfusion defect was smaller in patients older than 50 years than in patients age 50 years or younger ($14 \leq 7\%$ vs $41 \leq 8\%$, $p < 0.001$).

We conclude that the perfusion defect is small in patients with $< 70\%$ stenosis of the left anterior descending coronary artery, but varies considerably in patients with $\geq 70\%$ stenosis. Age is the chief determinant of perfusion defect size in patients with similar left anterior descending coronary artery anatomy and exercise variables. Age and, conceivably, the duration of disease may affect the functional maturity of collaterals. The data indicate that left anterior descending coronary artery lesions may well put into risk more than 30\% of the heart muscle in a great number of patients. This phenomenon is significantly more common in patients younger than age 50 years.

ALTHOUGH coronary atherosclerosis involving only one major vessel is usually associated with a good prognosis,$^1$ isolated stenosis of the left anterior descending coronary artery may be more serious than isolated disease of the right or circumflex arteries.$^2$ Several studies show that the annual mortality attributed to isolated left anterior descending disease treated medically is higher than that for isolated disease of the other two vessels.$^6$ An angiographic study of a group of 79 patients resuscitated from sudden death showed that 14 of these patients had isolated left anterior descending disease.$^7$

The optimal management of patients with isolated left anterior descending disease is controversial,$^8$ although a surgical survival rate of 98\% at a mean follow-up of 67 months has been reported.

Previous studies show considerable variation in the perfusion and function of the left ventricle at rest and during stress in patients with left anterior descending disease.$^{10-13}$ Assessment of the size of jeopardized myocardium may help to identify those patients with left anterior descending disease at higher risk of severe left ventricular dysfunction in the event of a myocardial infarction and, hence, a poorer prognosis.

Exercise thallium-201 imaging has been reported to be useful in assessing the viability of myocardium,$^{11,14}$ and several quantitative approaches have been used.$^{11,15-17}$

In this study we assessed the extent of jeopardized myocardium in patients with left anterior descending disease to determine predictors of the size of perfusion defects in these patients. Such findings may have important diagnostic and therapeutic implications.

Methods

Thirty-five patients with one-vessel left anterior descending disease without a history or electrocardiographic evidence of myocardial infarction who had exercise thallium-201 perfusion imaging within 3 months before coronary angiography constituted the study group. All patients were evaluated for symptoms of angina pectoris. No patient had unstable angina. All but one patient had symptoms of angina pectoris of less than 2 years' duration. Thirty were men and five were women, ages 34–66 years (mean 54 years). None of the patients had concomitant valvular or congenital heart disease and none had had prior bypass surgery.

Left- and right-heart catheterization, left ventriculography and coronary arteriography were performed with standard techniques. Each coronary vessel was visualized in multiple projections, including sagittal oblique projections. Each patient had at least 50\% diameter narrowing of the left anterior descending coronary artery. The lesion was described according to its location in relation to the first septal perforator and diagonal branches. None of these patients had multiple stenoses. Depending on the distribution of the artery, it was classified as dominant, usual or diminutive.$^{18}$ A
dominant left anterior descending coronary artery turns around the apex of the ventricle and continues as the posterior ascending artery, providing perforator branches to the inferior surface of the septum. A diminutive left anterior descending coronary artery fails to reach the apex of the heart, and in fact terminates midway anteriorly between the base and the apex.

Collaterals were considered present if collateral flow partially or completely opacified the disease vessel beyond the site of occlusion or narrowing. The left ventriculogram was assessed qualitatively for wall motion abnormalities; none of the patients had akinetic or dyskinetic segments. The angiograms were reviewed by two experienced angiographers without knowledge of the other test results, and the interpretations of both reviewers were used.

Each patient underwent multistage treadmill exercise testing in the fasting state in accordance with the Bruce protocol. The ECG was monitored continuously during exercise (leads V1, V3, and aVF) and the blood pressure was obtained by the cuff method every 2 minutes during stress and recovery. The exercise was continued until the patient complained of severe angina; 2 mm or more ST depression with or without angina, excessive fatigue, leg weakness or shortness of breath; or when we observed hypotension, frequent premature ventricular complexes or ventricular tachycardia. At peak exercise, 2 mCi of thallium-201 was injected intravenously, and the patient was asked to continue exercising for 30–60 seconds more.

Ten minutes after the exercise terminated, images were obtained in three projections. The techniques of exercise testing and imaging and interobserver and intraobserver variability in interpreting images have been described in detail. Redistribution images were obtained 4 hours after exercise in the projections that showed the perfusion abnormalities. All patients in the study with initially abnormal images showed partial or complete redistribution.

The size of the defect was expressed as a percentage of the total ventricular perimeter in each projection (fig. 1). The regions of the valves were excluded. This method is similar to that used by Field et al. to assess the extent of akinetic-dyskinetic segments by means of contrast left ventriculograms and has been used to measure the size of the thallium defects. The average percentage of abnormal perimeter was determined from the three projections. The interobserver variability in sizing the defect was 4 ± 4% (mean ± sd). The maximal difference was 13% in a patient with a large defect. Reproducibility of the quantitative analysis was examined in 10 patients with abnormal images on two occasions; the mean difference was 3 ± 3%.

**Statistical Analysis**

Statistical analysis was performed by the t test or analysis of variance when appropriate. Comparison between two variables was done using linear regression analysis. The Fisher exact test was used when

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![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Exercise thallium-201 images in three projections in a patient with severe disease of the left anterior descending coronary artery. Perfusion defects are seen in the 30° and 65° left anterior oblique (LAO) projections. The method for measuring the percentage of abnormal perimeter is shown. The dotted lines represent the perfusion defect, which is expressed as a percentage of the outer perimeter, excluding the valve areas. The 4-hour delayed images are shown. Also shown are the circumferential radial activity profiles from the initial and delayed images. The area of perfusion abnormalities are indicated on the curves.
TABLE 1. Comparison of Anatomic and Exercise Data According to Perfusion Defects

<table>
<thead>
<tr>
<th></th>
<th>Large perfusion defects (n = 12)</th>
<th>Small-moderate perfusion defects (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 9</td>
<td>58 ± 5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>9 (75)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>Women</td>
<td>3 (25)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Propranolol therapy</td>
<td>6 (50)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>LV wall motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (33)</td>
<td>4 (28)</td>
</tr>
<tr>
<td>Mild hypokinesia</td>
<td>8 (67)</td>
<td>10 (71)</td>
</tr>
<tr>
<td>LAD anatomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual</td>
<td>10 (84)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>Dominant</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Diminutive</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Site of stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>7 (58)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Middle</td>
<td>4 (33)</td>
<td>4 (28)</td>
</tr>
<tr>
<td>Distal</td>
<td>1 (8)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>90 ± 10</td>
<td>88 ± 12</td>
</tr>
<tr>
<td>Presence of collaterals</td>
<td>6 (50)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Rest HR (beats/min)</td>
<td>67 ± 10</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Exercise HR (beats/min)</td>
<td>140 ± 23</td>
<td>135 ± 31</td>
</tr>
<tr>
<td>Rest SBP (mm Hg)</td>
<td>136 ± 27</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>Exercise SBP (mm Hg)</td>
<td>165 ± 30</td>
<td>163 ± 26</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>8.2 ± 2.5</td>
<td>8.2 ± 2.9</td>
</tr>
<tr>
<td>Positive exercise ECG</td>
<td>7 (58)</td>
<td>9 (64)</td>
</tr>
</tbody>
</table>

Abbreviations: LV = left ventricular; LAD = left anterior descending coronary artery disease; HR = heart rate; SBP = systolic blood pressure.

comparing proportions. Stepwise linear regression was performed with the BMPD statistical program on variables to identify the variables that best predict the size of perfusion defect. A p value < 0.05 was considered significant.

Results

Coronary Anatomy

Twenty-six of 35 patients had ≥ 70% narrowing of the left anterior descending coronary artery (group 1) and nine had < 70% (but < 50%) diameter narrowing (group 2). The remaining coronary vessels were either normal or had < 30% stenosis. In group 1, the location of the lesion was proximal to both the first septal perforator and diagonal branches in 16 patients, between the first septal and diagonal branch in eight, and distal to both branches in two patients. In group 2, the lesion was proximal to the first septal and diagonal branches in two patients, between the two branches in two and distal to both branches in five (table 1).

Collaterals were present in 13 of 26 patients (50%) in group 1, but not in any patients in group 2. The left anterior descending coronary artery anatomy was of the usual type in 31 patients, of the dominant type in three and of the diminutive type in one patient. (This last patient was in group 2.)

Exercise Testing Results

The exercise ECG was positive in 19 patients (54%) (16 in group 1 and three in group 2), while 31 patients (89%) had exercise-induced thallium perfusion defects (25 in group 1 and six in group 2).

Size of Perfusion Defects

The defect was smaller in group 2 patients than in group 1 patients (10 ± 9% vs 27 ± 15%, p < 0.01) (fig. 2). Among patients with ≥ 70% stenosis (group 1), the size of the defect did not correlate with exercise heart rate (fig. 3). Depending on the size of the perfu-
Correlation between the size of the perfusion defect and peak exercise heart rate in 26 patients with ≥ 70% stenosis of the left anterior descending coronary artery.

In patients older than 50 years, the thallium defect was smaller in those with collaterals than in those without collaterals (14 ± 7% vs 24 ± 13%, NS).

TABLE 2. The Results in Relation to the Presence or Absence of Collaterals

<table>
<thead>
<tr>
<th></th>
<th>Pts with collaterals (n = 13)</th>
<th>Pts without collaterals (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 8</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Location of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before S₁ and D₁</td>
<td>8 (62)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Between S₁ and D₁</td>
<td>5 (38)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>After S₁ and D₁</td>
<td>0 (0)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>95 ± 8</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>Exercise HR (beats/min)</td>
<td>127 ± 26</td>
<td>149 ± 26</td>
</tr>
<tr>
<td>Exercise SBP (mm Hg)</td>
<td>161 ± 30</td>
<td>170 ± 30</td>
</tr>
<tr>
<td>Propranolol therapy</td>
<td>11 (85)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Size of perfusion defect (%)</td>
<td>28 ± 15</td>
<td>27 ± 13</td>
</tr>
</tbody>
</table>

Abbreviations: S₁ = first septal perforator; D₁ = first diagonal branch; HR = heart rate; SBP = systolic blood pressure.

Despite the lower heart rate in patients receiving propranolol therapy than in those not receiving such therapy (129 ± 28 vs 147 ± 24 beats/min), the size of the perfusion defect was not statistically different in the two groups (26 ± 17% vs 28 ± 13%). The results in the 26 patients with ≥ 70% stenosis in relation to the presence or absence of collaterals are summarized in table 2. The size of the perfusion defect was similar in patients with and without collaterals, even though patients with collaterals had more severe...
stenoses and lower exercise heart rates than those without collaterals.

The disease in 24 of the 26 group 1 patients was proximal — either before or between the first septal and first diagonal branches. Moreover, only one patient had a diminutive left anterior descending coronary artery. Therefore, our data did not allow us to analyze the effect of more distal disease on the size of the perfusion defect.

Using a multivariate stepwise regression analysis of 30 clinical, angiographic, electrocardiographic, exercise and scintigraphic variables (table 3), only age correlated significantly with the size of the perfusion defect, and no combination of other variables improved the prediction. The variables with the highest predictive value are shown in table 4. Only the age of patients showed significant correlation with the size of the defect. In fact, among the 26 group 1 patients, all 14 patients with small or moderate defects (≤ 30%) were older than 50 years of age, whereas eight of 12 with large defects (< 30%) were 50 years or younger (p = 0.0003).

**Table 3.** Variables Evaluated by Stepwise Regression Analysis

1. Age (years)
2. Sex
3. Duration of angina pectoris
4. Severity of angina pectoris (New York Heart Association classification)
5. History of hypertension
6. History of diabetes mellitus
7. History of cigarette smoking
8. Family history of premature atherosclerosis
9. Medications: nitrates
10. Medications: β blockers
11. Rest ECG normal; ST-T changes
12. Rest heart rate (beats/min)
13. Rest blood pressure (mm Hg)
14. Exercise heart rate (beats/min)
15. Exercise blood pressure (mm Hg)
16. Change in systolic pressure (from rest to exercise) (mm Hg)
17. Exercise duration
18. Exercise work load
19. Angina during exercise
20. Arrhythmias during exercise
21. Exercise electrocardiographic changes
22. Reason for termination of exercise
23. Exercise double product
24. Degree of stenosis
25. Location of stenosis
26. Type of left anterior descending artery
27. Presence or absence of collaterals
28. Left ventricular size
29. Left ventricular ejection fraction
30. Left ventricular wall motion

**Table 4.** Correlation Matrix of Variables Used to Predict Thallium Perfusion Defect Size in Group 1 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>( R^2 )</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.34</td>
<td>−0.58</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td>0.08</td>
<td>0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise HR (beats/min)</td>
<td>0.07</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise HR ( \times ) SBP (beats/min) (mm Hg)</td>
<td>0.06</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise SBP (mm Hg)</td>
<td>0.01</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>0.00</td>
<td>−0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: Ex HR = exercise heart rate; SBP = systolic blood pressure; HR \( \times \) SBP = rate-pressure product.

**Discussion**

The results of this study suggest that patients with \( \geq 70\% \) stenosis of the left anterior descending coronary artery have larger exercise perfusion defects than patients with stenosis of 50–69%. However, patients with one-vessel left anterior descending disease with obstructions \( \geq 70\% \) formed a heterogeneous group. Since the amount of jeopardized myocardium in this subset of patients is important prognostically and therapeutically, we sought the factors that would explain the variation in the amount of jeopardized myocardium in these patients.

There is considerable controversy whether fairly asymptomatic patients with coronary artery disease should undergo revascularization to preserve left ventricular function. Bypass surgery is generally not recommended for obstruction of the right coronary or circumflex artery unless the patient has disabling symptoms despite optimal medical therapy. On the other hand, some have recommended that young patients with high-grade obstruction of the proximal left anterior descending coronary artery undergo coronary bypass surgery, because it is assumed that a significant obstruction of the left anterior descending artery before the takeoff of any perforator or diagonal branches may compromise as much as 50% of the left ventricular myocardium, whereas a more distal lesion may compromise only 15%.21 However, whether younger patients with coronary anatomy similar to that of older patients would have a more favorable outcome with surgery remains to be shown. The goal of coronary bypass surgery in these circumstances is to preserve the viability of the myocardium. Therefore, if surgery is contemplated, each patient should be evaluated individually, considering the mass of myocardium in jeopardy.

Assessing the amount of myocardium in jeopardy by thallium is important. The exact correlation between the size of the perfusion defect measured by exercise images and the subsequent size of scar tissue after infarction is not clear; however, patients with larger defects are at higher risk of larger infarctions than patients with smaller defects.22 There is great variability in thallium defect size in patients after infarction; larger defects denote more severe left ventricular decompensation and a poorer prognosis.23
Stepwise linear regression showed that only the age of the patient correlated directly with the size of the perfusion abnormality when other factors, such as sex, severity of stenosis, location of stenosis, collateralization, and exercise end points, were analyzed. In 24 of the 26 patients with \( \geq 70\% \) stenosis, the lesion was proximal, either before or between the first septal perforator and first diagonal branches (table 1). Our data, therefore, did not allow us to compare patients with proximal disease to those with more distal disease. All patients with premature coronary disease (younger than 50 years) had large perfusion defects on exercise scans.

Why should age influence the extent of perfusion abnormality when left anterior descending anatomic disease and exercise end point are similar in age groups? Cabin and Roberts\(^2\) did not show a correlation between infarct size at necropsy and patient age, or between the amount, location, and extent of coronary arterial narrowing by atherosclerotic plaque and age. However, their findings did not pertain solely to one-vessel disease. Similarly, although duration of anginal symptoms tends to produce larger epicardial collaterals,\(^25\)\(^,\)\(^26\) we found no difference in the degree of these anastomoses relating to age. All but one patient had had angina for less than 2 years. However, in humans, subendocardial collaterals (which may not be visualized angiographically) are more numerous than subepicardial collaterals,\(^27\)\(^,\)\(^28\) so that one cannot discount the possibility of more extensive development of subendocardial collaterals in elderly patients or those with small perfusion defects. Age may affect the maturity and extent of subendocardial and intramural coronary blood vessels simply because atherosclerosis has had more time to evolve in elderly patients. The influence of epicardial collaterals may be less important.

Another factor that may be important is exercise-induced spasm, which limits coronary blood flow and causes exercise perfusion abnormalities.\(^29\)\(^,\)\(^30\) The arteries of younger patients may be more vulnerable to coronary vasospasm, but the lack of an ST elevation with exercise in our patients makes this possibility less likely.

Since thallium distribution is related not only to regional blood flow but also to the efficiency of ionic exchanges by myocardial cells, the process of aging could affect the distribution of the thallous ion.

Madden et al.\(^31\) studied the effects of aging on the washout kinetics of thallium in rats using a three-compartment model (extracellular, intracellular and subcellular), and found a significant reduction in the extracellular compartment and an increase in the subcellular compartment in older rats. The clinical significance of this finding is not clear, but it appears that aging affects thallium distribution in the myocardium.

Two potential problems of this study should be considered: the coronary angiograms and the thallium images. Factors other than the degree of stenosis and collaterals may affect the flow: the actual lumen at the site of stenosis, which depends on the caliber of the vessel, the eccentricity of the lesion, and the length of the stenosis.\(^32\)\(^-\)\(^34\) All left anterior descending vessels in this study were considered to be of normal caliber (at least 2 mm in diameter); furthermore, the length of the stenosis appears to be much less important than the degree of stenosis. The coronary angiograms were interpreted qualitatively by two experienced angiographers, but quantitative measurements using biplane angiograms were not available; however, the latter method is seldom used routinely.

Determination of thallium defect size is subject to problems of superimposition, attenuation, resolution and early redistribution; but all of our images were obtained by the same method and in the same sequence of projections, so the variability of defect size cannot be ascribed to this problem alone. The real problem is the absence of an independent method to measure the size of ischemic myocardium. Within the abnormal perfusion segment, the radionuclide uptake could be mildly, moderately or severely reduced, or could be absent. The importance of the degree of the perfusion deficit vs the extent of the perfusion deficit is not clear. Quantitative analysis of the thallium images by circumferential radial activity\(^17\) profiles does not appear to have an advantage in this type of study (although they were available in most patients). This technique has an advantage in patients with multivessel disease in ascertaining perfusion abnormalities in apparently normal segments (based on an abnormal washout pattern). The reliability of washout curves, moreover, depends heavily on the method of background subtraction, which has its own limitations.\(^35\)

**Clinical Implications**

Our results indicate that patients with isolated left anterior descending disease should not be lumped together, and the functional consequences of this disease should be considered. The data indicate that left anterior descending lesions may well put into risk more than 30% of the heart muscle in many patients. This phenomenon is significantly more common in patients younger than age 50 years. Our choice of 30% defect size was based on observations that damage of more than 30% of the myocardium is likely to result in cardiogenic shock or heart failure in patients with acute infarction.\(^36\) Further studies are needed to find out why older patients have smaller exercise-induced defects than younger patients and to determine the prognostic implications of the size of the exercise-induced perfusion defects.

**References**

5. Kouchoukos NT, Oberman A, Russell RO Jr, Jones WB: Surgical versus medical treatment of occlusive disease confined to the left
antior descending coronary artery. Am J Cardiol 35: 836, 1975
7. Angell CS, Griffith LSC: Anteroseptal myocardial ischemia as a cause of ventricular fibrillation or tachycardia. (abstr) Circulation 54 (suppl II): II-173, 1976
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