Influence of coronary collateral blood flow on the development of exertional ischemia and Q wave infarction in patients with severe single-vessel disease

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ABSTRACT The functional significance of coronary collateral flow from a nonobstructed supply artery was studied in 121 patients with severe (≥80%) single-vessel disease, 64 with and 57 without Q wave infarction. All patients underwent exercise thallium imaging and coronary angiography. On angiography, collateral flow was present in 85% of 74 occluded arteries compared with only 17% of 47 arteries with subtotal obstruction (p < .001). Collateral flow was not seen in arteries with lesions of less than 90% obstruction. Collateral flow was present in 100% of 29 occluded arteries in patients without Q wave infarction compared with only 76% of 45 occluded arteries with Q wave infarction (p < .005). Clinical variables did not correlate with collateral flow. Collateral flow did not prevent ischemia on exercise thallium imaging in patients without Q wave infarction: 30 of 33 (91%) with collateral flow had reversible thallium defects compared with 24 of 24 (100%) without collateral flow (p = NS). In patients with Q wave infarction, partially reversible exercise thallium defects (peri-infarctional ischemia) were more common with flow to the area from either subtotal obstruction (73%) or collateral flow (45%) than with no flow from total occlusion (27%; p = .05). In patients with severe single-vessel disease the presence of collateral flow is principally determined by coronary occlusion. Collateral flow may protect from Q wave infarction but does not prevent exercise ischemia on thallium imaging.


THE FUNCTIONAL significance of coronary collateral vessels visualized at angiography remains controversial, despite a large number of studies. These studies have produced conflicting findings as to whether collateral blood flow protects the myocardium from exercise-induced ischemia, varying from complete or partial protection to no protection or an increased incidence of ischemia. Differences in patient selection and methodology may explain some of these discrepancies. Most studies were in patients with multivessel disease, making it difficult to distinguish between ischemia in the distribution of the collateralized and the noncollateralized vessel and introducing the variable effect of obstruction in the vessel supplying collaterals.

In this study we selected patients with severe obstruction in only one major coronary artery so that the functional significance of collateral blood flow could be assessed without the interference of ischemia in another area or obstruction in the vessel supplying collaterals.

Methods

Patient selection. Over a 4 year period 121 patients with severe (80% or greater luminal diameter reduction) single-vessel coronary artery disease were referred for exercise thallium imaging and coronary angiography. There were 114 men and seven women with a mean age of 50 ± 7 years (SD) (range 32 to 65). Q wave infarction, defined by pathologic Q waves on the resting 12-lead electrocardiogram (ECG), was present in 64 and absent in 57 of the patients. Of the 57 patients without Q wave infarction, 32 had a previous history of either unstable angina or subendocardial infarction. Subendocardial infarction was defined as ischemic chest pain lasting longer than 30 min associated with a rise in creatine kinase level to greater than twice normal, without development of pathologic Q waves. Unstable angina was defined as rest pain requiring hospital admission, with no rise in creatine kinase level or development of pathologic Q waves.

Exercise electrocardiography. All patients underwent exercise electrocardiography combined with myocardial thallium-
201 imaging. Patients exercised maximally on an upright bicycle ergometer according to a graded multistage continuous protocol until chest pain, breathlessness, or fatigue occurred. Leads were placed in the standard location recommended by Mason et al., and a 12-lead ECG was recorded before and during each minute of exercise and recovery with an Avionics three-channel recorder. The ECGs were interpreted by two independent observers. The exercise ECG was considered positive if there was 1 mm or greater horizontal or downsloping ST segment depression lasting 0.08 sec in 3 consecutive beats.

Myocardial perfusion imaging. At peak exercise 1.5 to 2.0 mCi of thallium-201 were injected intravenously, and the patients continued exercising for another minute to enable blood clearance and myocardial uptake of the thallium during conditions of stress. Imaging was begun in the exercise laboratory within 10 min after the administration of thallium-201 (exercise scan). With a mobile gamma camera and low-energy, all-purpose, parallel-hole collimator, four views were taken: anterior, 40 and 60 degree left anterior oblique views with the patient supine, and left lateral view with the patient in the right decubitus position. In the first view, 400,000 counts were collected. Counts in the other three views were taken in an equal time. The four scans were completed within 40 min of exercise. Scans were repeated by the same method 4 hr later in the same four views (4 hr redistribution scan).

The scans were interpreted from the original Polaroid scintiphotographs without computer enhancement or background subtraction by three unbiased experienced observers. Exercise and 4 hr redistribution scans were analyzed for the presence or absence of a thallium defect. A defect was considered reversible if there was a decrease in either its size or intensity in the 4 hr redistribution scan. Defects were categorized as either totally or partially reversible depending on whether the 4 hr scan returned completely to normal. A consensus of opinion of the three observers was taken, with an interconsensus variability of 7%.

Coronary arteriography and left ventriculography. Selective coronary arteriography was performed in multiple projections by the Judkins or Sones technique. Each study was reviewed by two observers independent of the exercise electrocardiographic and thallium scan data. Stenoses were graded subjectively by visual assessment of the cincangiograms, and a consensus of the two observers was taken for the degree of stenosis and the presence of coronary collateral flow. Severe single- vessel coronary artery disease was defined as 80% or greater luminal diameter reduction in only one coronary artery, and no lesion of 50% or greater in the other two vessels. Coronary collateral flow was classified as present when the artery distal to a stenosis or occlusion was opacified by injection of the contralateral coronary artery and as absent when no distal opacification was seen. Collateral flow was also deemed present when injection of the left coronary artery opacified the vessel distal to an occlusion in either the left anterior descending or circumflex coronary artery.

Antegrade flow after injection of the affected artery was classified on a five-point scale: 1, normal flow; 2, slightly reduced contrast density or delayed washout; 3, marked reduction of contrast density or delayed washout with a good distal vessel; 4, marked reduction of contrast density or delayed washout with a small distal vessel; and 5, no antegrade flow. Left ventricular wall motion in the area of myocardium supplied by the diseased vessel was described as normal, hypokinetic, or akinetic.

The involved artery was the left anterior descending in 70 patients (31 with and 39 without Q wave infarction) and the right coronary or left circumflex artery in 51 patients (33 with and 18 without Q wave infarction).

Statistical analysis. Analysis of difference of proportions was performed with a chi-square test or Fisher’s exact test. Student’s t test was used to analyze group difference of continuous variables.

Results

Relationship of collateral flow to occlusion and Q wave infarction. The major factor for the development of collateral flow was the presence of occlusion: collateral flow was present in 63 of 74 (85%) occluded arteries compared with only eight of 47 (17%) arteries with subtotal obstruction (p < .001). Collateral flow was not present in any artery with stenosis less than 90%. There was no significant difference between the proportion of left anterior descending arteries (40/70, 57%) and right or left circumflex arteries (31/51, 61%) showing collateral flow.

In patients with Q wave infarction, the affected coronary artery was totally occluded in 45 of 64, with collateral flow present in 34 of the 45 occluded arteries (76%). In contrast, in patients without Q wave infarction, the affected artery was occluded in 29 of 57, and all 29 (100%) showed collateral flow (p < .005 vs Q wave infarction). The proportion of patients with Q wave infarctions showing collateral flow was similar for anterior (left anterior descending) infarcts (16/31, 52%) and inferior (right coronary or left circumflex) infarcts (22/33, 66%; p = NS). The same was true for Q wave infarction associated with an occluded vessel: 19 of 23 (83%) with anterior infarction showed collateral flow compared with 15 of 22 (68%) with inferior infarction (p = NS).

Patients without Q waves

Clinical and angiographic comparisons (table 1). In the group of 57 patients without Q wave infarction, collateral flow was present in 33 (29 with total occlusion) and absent in 24 (all with subtotal obstruction). There was no difference in the mean age, serum cholesterol level, or smoking status between the two groups (table 1). There was a similar proportion of patients with a history of angina for more than 1 month in both groups.

The prevalence of previous subendocardial infarction or unstable angina was similar in patients with and without collateral flow (52% vs 63%). Considered separately, subendocardial infarction was more likely to have occurred in patients with collateral flow (33% vs 8%; p < .05) and was accompanied by a greater prevalence of akinetic segments on the left ventriculogram. Almost a quarter of patients (7/29) with total occlusion had normal left ventriculograms and no history of subendocardial infarction. Because of the high proportion
of occluded arteries, the mean antegrade flow score was worse in the group with collateral flow.

Exercise test comparisons (table 1). The results of exercise stress testing and thallium imaging were similar in the groups with and without collateral flow. A positive exercise ECG was obtained in 67% of patients with and 75% without collateral flow (p = NS). Nearly all the patients in both groups (91% and 100%) had a reversible thallium defect and in almost half (42% and 54%) the defect showed complete redistribution on the 4 hr scan. The coronary angiogram and exercise thallium images from a patient with collateral flow and a reversible thallium defect are shown in figures 1 and 2. Patients with previous subendocardial infarction or unstable angina were more likely than those without to show partially reversible defects (19/32 [59%] vs 8/25 [33%]; p < .05). Only two patients, both with collateral flow, did not show an exercise thallium defect, and in one of these the exercise ECG was positive.

Patients with Q wave infarction. Collateral flow was present in 38 (59%) of the 64 patients with Q wave infarction and absent in 26 (41%). Thirty-four of the 38 patients with collateral flow (89%) had total occlusion of the artery. Of the 26 patients without collateral flow, 11 had total occlusion and 15 had subtotal obstruction.

The clinical, angiographic, and exercise data for the patients with Q wave infarction with and without collateral flow are shown in table 2. There were no significant differences in the age, cholesterol level, smoking status, antegrade flow score, and the proportion with akinetic segments between the two groups.

On exercise stress testing, between 23% and 31% developed either angina pectoris or a positive exercise ECG, but there were no differences between the two groups (table 2). All patients showed a thallium defect on the stress image. The defect was constant in 52% and partially reversible in the remainder. The two groups did not differ in the proportion of partially reversible defects. When the patients without collateral flow were further subdivided into those with subtotal obstruction and those with occlusion and compared with patients showing collateral flow, there was a difference in the proportion with partially reversible defects: 73% of patients with subtotal obstruction and no collateral flow had partially reversible defects compared with 45% of patients with collateral flow and 27% with occlusion but no collateral flow (p = .05).

TABLE 1
Patients without Q waves: comparison between those with and without collateral flow

<table>
<thead>
<tr>
<th></th>
<th>Collaterals (n = 33)</th>
<th>No collaterals (n = 24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50 ± 8</td>
<td>49 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>22 (67%)</td>
<td>14 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>7.2 ± 1.6</td>
<td>6.5 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Angina &gt;1 mo</td>
<td>20 (61%)</td>
<td>15 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>UAP or SEI</td>
<td>17 (52%)</td>
<td>15 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>UAP</td>
<td>6 (18%)</td>
<td>13 (54%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>SEI</td>
<td>11 (33%)</td>
<td>2 (8%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>LV akinesis</td>
<td>10 (30%)</td>
<td>2 (8%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Artery occluded</td>
<td>29 (88%)</td>
<td>0 (0%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Antegrade flow (score)</td>
<td>4 ± 1</td>
<td>2 ± 1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ex ECG positive</td>
<td>22 (67%)</td>
<td>18 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ex angina</td>
<td>24 (73%)</td>
<td>18 (75%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Unless otherwise specified, data are n values.

UAP = unstable angina pectoris; SEI = subendocardial infarction; LV = left ventricular.

FIGURE 1. Coronary angiogram of a patient without Q wave infarction. Top, Injection of left coronary artery in right anterior oblique view, with occlusion of the left anterior descending artery. Bottom, This artery fills from collaterals after injection of the right coronary artery.
FIGURE 2. Exercise (EX) and 4 hr redistribution thallium scan (R) from the same patient as in figure 1. There is a defect in the anteroseptal and apical segments that is totally reversible on the 4 hr scan.

Discussion

Protection from Q wave infarction. Although considerable controversy surrounds the functional significance of coronary collaterals, there is general agreement that collateral blood flow may protect the heart from transmural infarction. This conclusion is underscored by the frequent finding of preserved wall motion and absence of morphologic infarction in areas of myocardium supplied by totally occluded vessels. In our study collateral flow was present in all patients with an occluded artery but no Q waves, whereas all patients with a totally occluded artery without collateral flow had Q wave infarction. Although collaterals may help prevent Q wave infarction when a vessel occludes, full collateral development in experimental animals requires gradual stenosis of the vessel. The situation in patients with occluded vessels and no infarction may be analogous to this model, but the speed of occlusion cannot be ascertained. At least the duration of angina was not different in the patients with and without collateral flow.

Myocardial infarction in man is frequently a sudden event resulting from coronary thrombosis, plaque hemorrhage, or spasm, and collateral blood flow may not have time to develop. Many of our patients with Q wave infarction and total occlusion of the vessel showed good collateral blood flow. Angiographic studies of myocardial infarction within 6 hr of the onset of symptoms showed that collaterals are present in almost two-thirds of patients with an occluded vessel and may reduce infarct size and preserve myocardial function, but it is not possible to say whether this develops before or after the infarction.

Protection from exertional ischemia in patients without Q waves. Early studies on the role of coronary collaterals in preventing exertional ischemia relied on angina and ST segment changes to assess ischemia and showed either a greater incidence of exertional ischemia in patients with collaterals or protection from inferior ischemia by collaterals in some patients. The inability of ST segment depression on the exercise ECG to locate the anatomic site of ischemia makes interpretation of the results difficult. Because these studies included patients with multivessel disease, ischemia in the distribution of collateralized and non-collateralized vessels cannot be distinguished. Thallium imaging can better locate ischemic areas but introduces different problems in patients with multivessel disease or previous infarction. Ischemia in a particular vascular distribution may be missed when there are defects caused by ischemia or infarction in another vascular area, which could account for collateral flow appearing to prevent ischemia in some studies. Conversely, because of lack of anatomic specificity, defects in the watershed area of the apex have been disregarded and could result in underestimation of ischemia in a collateralized area. It is not surprising that thallium studies of collateral function have yielded conflicting results, varying from the prevention of thallium defects in some patients to an increased incidence of defects.

In this study we attempted to overcome the problems of previous studies by selecting patients with severe obstruction in only one vessel and by considering separately patients with and without Q wave infarction.

**TABLE 2**

<table>
<thead>
<tr>
<th>Findings in patients with Q wave infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collaterals</strong></td>
</tr>
<tr>
<td><strong>Ex (yr)</strong></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
</tr>
<tr>
<td>Smokers (%)</td>
</tr>
<tr>
<td>Antegrade flow (score)</td>
</tr>
<tr>
<td>LV akinesis (%)</td>
</tr>
<tr>
<td>Ex angina (%)</td>
</tr>
<tr>
<td>Ex ECG positive (%)</td>
</tr>
<tr>
<td>Ex 201TI scans</td>
</tr>
<tr>
<td>Partially reversible defect (%)</td>
</tr>
</tbody>
</table>

Unless otherwise specified, data are n values.
LV = left ventricular.
Our results indicate that the presence of collateral flow does not prevent exercise-induced ischemia as judged by thallium imaging. Reversible thallium defects were almost invariably present after exercise in the patients with collateral flow. Only one other study\(^\text{40}\) included patients with single-vessel disease and found positive exercise ECGs more common in patients with collaterals (94% vs 71%; \(p = \text{NS}\)). Not all patients in that study underwent thallium scintigraphy, but six of 10 patients with collaterals did not have thallium defects despite a positive exercise ECG in five. The reason for the negative thallium images in these patients is not clear, given that there was electrocardiographic evidence of ischemia.

The high incidence of exercise-induced ischemia in the distribution of collateralized arteries may be due to the severe underlying lesions present. In our patients without Q waves, collateral flow was found only in vessels with a stenosis of 90% or greater, and the majority of arteries were totally occluded. Moreover, occlusion was not seen without collateral flow. This is in agreement with earlier results\(^\text{8, 23-25}\) and highlights the difficulty of selecting vessels with equal severity of obstruction or occlusion with and without collateral flow for comparison of collateral function.\(^\text{20}\)

Hemodynamic and flow measurements during balloon inflation at coronary angioplasty provide a unique assessment of coronary collateral function and may help explain why collateral flow does not prevent exercise ischemia. The residual great cardiac vein flow during occlusion of the left anterior descending artery is higher in the presence than in the absence of collateral flow,\(^\text{26}\) and the distal occluded pressure is greater in patients with occlusions or high-grade stenoses with collateral flow compared with that in patients without collateral flow (33 and 30 mm Hg vs 18 mm Hg, respectively),\(^\text{27}\) indicating a significant contribution of collateral flow at rest. Although this distal occluded pressure may be adequate at rest when left ventricular diastolic pressure is low, the transmural pressure gradient is reduced during exercise when the left ventricular diastolic pressure rises\(^\text{28}\) and would tend to reduce collateral flow. This may explain why collaterals visualized at rest either disappear or diminish during exercise-induced angina\(^\text{29}\) and why collateral flow did not prevent exercise-induced ischemia in the present study.

The usual problem with studies on collateral function during exercise is the selection bias introduced by inclusion of only symptomatic patients.\(^\text{20}\) These patients are referred for exercise stress testing and coronary angiography because of symptoms, and ischemia and inadequate collateral function are therefore likely. Asymptomatic men and women with coronary artery disease may not seek medical attention if protected from ischemia by adequate collateral flow. Our finding that collateral flow does not prevent from exercise-induced ischemia remains relevant for the usual clinical population of symptomatic patients.

**Clinical implications.** Coronary collateral flow seen at angiography usually denotes occlusion or hemodynamically severe stenosis in the affected vessel. Although collateral flow may protect some patients from Q wave infarction, it does not appear to prevent exercise-induced ischemia.

**References**

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S B Freedman, R F Dunn, L Bernstein, J Morris and D T Kelly

Circulation. 1985;71:681-686
doi: 10.1161/01.CIR.71.4.681

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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