Relation Between Myocardial Perfusion and Left Ventricular Function Following Acute Coronary Occlusion: Disproportionate Effects of Anterior vs. Inferior Ischemia

Ricky M. Schneider, Kenneth G. Morris, Alan Chu, Kenneth B. Roberts, R. Edward Coleman, and Frederick R. Cobb

This study examined the relation between left ventricular (LV) function and the severity of acute myocardial ischemia in a conscious dog model. The LV ejection fraction (EF) was measured by multigated equilibrium radionuclide angiography, and regional myocardial blood flow was measured with radioactive microspheres before and 10 minutes after distal and then proximal occlusion of the left anterior descending (LAD, 13 dogs) or left circumflex (LC, 13 dogs) coronary artery. Two methods were used to evaluate the extent of ischemia. The first method determined the mass of myocardium that was ischemic based on different degrees of reduced blood flow. The second method estimated the severity of ischemia expressed as blood flow deficit resulting from each coronary occlusion. Global LV function was very sensitive to ischemia, and the relation between change in function and the degree of ischemia were described best by linear functions. The best linear correlation between mass of ischemic myocardium and percent reduction in EF resulted from the ischemic region defined as all tissue with 25% or greater reduction in blood flow, \( r = 0.84 \) for LAD (\( Y = 0.96X + 1.8 \)) and \( r = 0.75 \) for LC (\( Y = 0.53X + 2.0 \)) occlusions. Defining ischemic mass by more severe reduction in blood flow resulted in exclusion of ischemic myocardium that affected function. The myocardial blood flow deficit also correlated linearly with percent reduction in EF, \( r = 0.89 \) for LAD (\( Y = 1.31X + 2.7 \)) and \( r = 0.81 \) for LC (\( Y = 0.83X - 0.1 \)) occlusions. The slope of the regression lines using both analyses of ischemia were significantly greater (\( p < 0.01 \)) for LAD than LC occlusions, indicating that for comparable degrees of ischemia LAD as compared to LC occlusion decreased EF to a greater extent. Calculation of EF from attenuated corrected volumes resulted in small changes in LAD, but not LC, EF and did not account for the disproportionate effects of LAD and LC ischemia. In a separate group of studies (\( n = 18 \)) EF measured by radionuclide angiography after LAD or LC occlusions correlated well with biplane contrast angiography \( r = 0.93 \), SEE 5.1. These data suggest that disproportionately greater effects of LAD compared to LC ischemia on global EF in the dog are due primarily to different pathophysiologic responses to ischemia. (Circulation Research 1987;60: 60–71)

Acute myocardial ischemia results in a prompt decrease in regional contraction that is related quantitatively to the reduction in regional myocardial blood flow. Previous studies have described decreases in left ventricular (LV) global function during graded restriction of coronary artery flow and greater decreases in LV function with proximal, then distal, coronary occlusions. Akaishi et al demonstrated a linear correlation between changes in LV function and the degree of ischemia. The best linear correlation between mass of ischemic myocardium and percent reduction in EF resulted from the ischemic region defined as all tissue with 25% or greater reduction in blood flow, \( r = 0.84 \) for LAD (\( Y = 0.96X + 1.8 \)) and \( r = 0.75 \) for LC (\( Y = 0.53X + 2.0 \)) occlusions. Defining ischemic mass by more severe reduction in blood flow resulted in exclusion of ischemic myocardium that affected function. The myocardial blood flow deficit also correlated linearly with percent reduction in EF, \( r = 0.89 \) for LAD (\( Y = 1.31X + 2.7 \)) and \( r = 0.81 \) for LC (\( Y = 0.83X - 0.1 \)) occlusions. The slope of the regression lines using both analyses of ischemia were significantly greater (\( p < 0.01 \)) for LAD than LC occlusions, indicating that for comparable degrees of ischemia LAD as compared to LC occlusion decreased EF to a greater extent. Calculation of EF from attenuated corrected volumes resulted in small changes in LAD, but not LC, EF and did not account for the disproportionate effects of LAD and LC ischemia. In a separate group of studies (\( n = 18 \)) EF measured by radionuclide angiography after LAD or LC occlusions correlated well with biplane contrast angiography \( r = 0.93 \), SEE 5.1. These data suggest that disproportionately greater effects of LAD compared to LC ischemia on global EF in the dog are due primarily to different pathophysiologic responses to ischemia. (Circulation Research 1987;60: 60–71)

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cardiac perfusion measured with radioactive microspheres, during acute left anterior descending or left circumflex coronary artery occlusion.

Materials and Methods
The studies were performed in chronically instrumented, awake dogs to avoid the variables of anesthesia and acute surgery.

Surgical Preparation
Twenty-six mongrel dogs weighing 16–30 kg were anesthetized with sodium thiamylal (30–40 mg/kg body weight) and underwent left lateral thoracotomy. Either the LAD or the LC coronary artery was freed by blunt dissection to permit placement of adjustable occluders. Polyethylene loop, snare-type occluders were placed loosely around the vessel and fastened securely to the epicardium. Thirteen dogs had snares placed on the LAD: one occluder was placed immediately after the first anterolateral branch (proximal snare) and a second occluder was placed beyond at least one other major anterolateral branch (distal snare) in all dogs; one dog had a third snare placed between the proximal and distal occluders. Thirteen dogs had occluders placed on the LC: a proximal occluder was placed after the first marginal branch in all dogs; a distal occluder was placed beyond at least one major marginal branch in 11 dogs.

Polyvinyl chloride catheters (3 mm o.d.) were filled with heparin and placed in the aortic arch through the left internal mammary artery and in the left atrium via the atrial appendage. A pacing electrode was sutured to the atrial appendage. A pacing electrode was sutured to the right atrial appendage. The snares were tunnelled to a ventral subcutaneous pouch at the base of the neck. Thirteen dogs had snares placed on the right atrial appendage. The snares were tunnelled to a dorsal pouch at the base of the neck. The animals were allowed to recover for 7–14 days before being studied.

Experimental Protocol
The pouches were anesthetized with lidocaine and the catheters, pacing electrode, and snares were exteriorized 1 day prior to or the morning before each study. All dogs received 5 mg morphine sulfate administered slowly i.v. before control studies, and 5 mg i.v. before proximal coronary occlusions to provide mild sedation and relieve chest pain resulting from the coronary occlusions.

Dogs were studied awake while lying loosely restrained on the right side. Aortic and left atrial pressure and electrocardiographic standard lead II were recorded on a Hewlett-Packard 8-channel recorder.

In the control state, hemodynamic measurements were recorded, RNA was performed in duplicate, and myocardial blood flow was measured by injection of radioactive microspheres. To provide a regular cardiac rhythm rather than the sinus arrhythmia of the conscious dog, the heart was paced from the right atrial appendage at a rate that slightly exceeded the resting sinus rate.

After the control measurements, the distal snare was occluded permanently. Hemodynamic recordings were made continuously. Beginning 10 minutes after distal occlusion, RNA was performed in duplicate and radioactive microspheres were injected. After completion of these studies, the proximal snare was permanently occluded. Beginning 10 minutes after proximal occlusion, RNA was again performed in duplicate and microspheres were injected. All studies were performed during atrial pacing just above the sinus rate except when an occlusion resulted in a sinus rate greater than approximately 120 beats/min.

Radionuclide Angiography
LV EFs measured by RNA in conscious dogs correlate closely in our laboratory with simultaneously obtained EFs measured with ultrasonic dimension crystals over a wide range of LV function. In the present study, RNA was performed after red cells were labeled in vivo with 30 mCi of technetium-99m. Data were acquired using a Siemens L.E.M. mobile scintillation camera (Siemens Co., Des Plaines, Ill.) with a high sensitivity parallel hole collimator and an r-wave triggered gate interfaced to a Medical Data Systems A2 computer. Studies were acquired in byte mode in a 64 x 64 matrix of 24 frames of 200,000 counts each, with a 1.48-fold magnification. Duplicate acquisitions were performed sequentially.

To define optimal LV separation from surrounding structures, preliminary studies were performed in 4 dogs in which multiple cobalt-57 markers were sutured to the left atrioventricular groove or at the epicardial borders of the right ventricle. Multiple static and dynamic images were recorded in various projections. These images demonstrated that the ventral position with slight caudal tilt and with the collimator parallel to the frontal plane viewed the ventricular septum tangentially and produced optimal LV separation. In this position, the lower portion of the left atrium overlies the upper part of the LV image.

LV EF was determined using a varying region of interest technique. Regions were assigned for each of the 24 frames of the recorded study using an operator-assisted edge detection program. Analysis of LV count rates in each frame allows construction of a time-activity curve and determination of the EF. The time-activity curve was corrected for background activity by subtracting the average number of counts per pixel in a manually assigned background region of interest from the left ventricular counts in each picture element of each frame. The background region was delineated with a joystick and was 5 pixels wide and approximately 2 pixels away from the inferior and lateral margins of the end-systolic LV region. End diastole and end systole were determined from the peak and trough of the time-activity curve. The EF was calculated by the formula:

\[
EF = \frac{N_{ED} - N_{ES}}{N_{ED}}
\]  

where \(N_{ED}\) is the background-corrected end-diastolic
count rate and $N_{ba}$ is the background-corrected end-systolic count rate.

**Attenuation-Corrected Radionuclide Angiography Ejection Fraction**

In recent studies from our laboratory, using LV models and theoretical analyses, we observed that ventricular regions close to the imaging device (i.e., anterior) influence the measured RNA EF greater than regions that are farther from the detector (i.e., posterior). We found that during regional hypokinesis the EF could be calculated accurately from attenuation-corrected absolute ventricular volumes. The attenuation compensation procedure described in previous reports was utilized in 10 of the dogs that had LAD coronary occlusions and 6 of the dogs that had LC occlusions.

**Myocardial Blood Flow**

Myocardial blood flow was determined by injecting carbonized microspheres, 9 ± 1 μm (mean ± SD) in diameter, and labelled with γ-emitting nuclides, 95Sr, 99Nb, 48Sc, or 113Sn. The microspheres were obtained as 1 mCi of each radionuclide in 10 ml of 10% dextran so that 1.0 ml, the volume injected, contained approximately 3 x 10^6 microspheres. Before each injection, the microspheres were mixed by agitation for at least 15 minutes in an ultrasonic bath (3M Co., Model DA0950) alternating with a Vortex agitator. A volume of 10 ml of the microsphere suspension was injected into the left atrium over a period of 10 seconds and the line flushed with 10 ml of isotonic saline. Beginning simultaneously with each microsphere injection and continuing for 90 seconds, a reference blood sample was collected from the aortic catheter in counting vials at a constant rate with a withdrawal pump. Serial injections of the microspheres resulted in no change in heart rate or in subsequently measured aortic or left atrial pressure.

After the animal was killed and the heart removed, the coronary artery occluders were released and the ostium of the left main coronary artery was cannulated with a polyethylene catheter and perfused with barium sulfate gel. The heart was then placed in 10% buffered formalin for at least 3 days to facilitate sectioning. The great vessels and atria were removed, and the heart was cut into 8 transverse rings. Radiographs were made of each ring, and the radiographs were used to trace the epicardial and transmural distribution of the occluded and nonoccluded vasculature. The medial and lateral margins of the distal and proximal ischemic or risk region were identified and sectioned.

After removal of right ventricle, epicardial fat, and major epicardial vessels, the regions at risk in each ring from distal and proximal coronary occlusions were weighed, divided into multiple sections, and subsectioned into 4 equal transmural layers, resulting in samples weighing approximately 1–2 g. Sections of myocardium were also cut from portions of each ring that were remote from the anatomic risk region to serve as nonischemic control samples. In 17 hearts, tissue samples approximately 3 mm wide were cut from immediately outside the medial and lateral borders of the proximal risk region in LV rings 2–7. These samples were cut into epicardial and endocardial halves, and blood flow was measured to assure that the apparent occluded region sampled contained all the ischemic tissue.

The radioactive activity in each reference blood and tissue sample was measured 14 days or more after occlusion in a Packard Gamma Scintillation Spectrometer (Canberra Industry, Inc., Meridian, Conn., Model 5912), using window settings selected to correspond with the peak energies of each radionuclide. Blood flow in each tissue sample was determined using counts/ml/min for the blood samples and the counts/min for the tissue samples. Blood flow was calculated using the formula:

$$Q_m = Q_r \cdot C_m/C_r$$

where $Q_m$ = myocardial flow (ml/min), $Q_r$ = reference blood flow (ml/min), $C_m$ = counts/min in myocardium, and $C_r$ = counts/min in reference blood flow. Myocardial blood flow (ml/min) was divided by the sample weight and expressed as ml/min/g.

**Data Analysis**

**Radionuclide Angiography.** Duplicate measurements of EF were made in all dogs in the control state and after coronary occlusions. Duplicate measurements were compared by calculating a mean difference between measurements and by linear regression analyses. Twenty-two RNA studies from 3 animals were independently analyzed by 2 different investigators. Interobserver variability was assessed by calculating the mean difference between measurements and by linear regression analysis.

Each EF value before and after occlusion represents the average of duplicate measurements. The percent change in EF resulting from each coronary occlusion was computed. The EF value obtained after occlusion was subtracted from the control value; this absolute change in EF was divided by the control value and expressed as a percent of control. An increase in EF after coronary occlusion was considered a zero change. The EF was slightly higher after occlusion in 6 dogs; the maximum increase was 7%.

**Myocardial Blood Flow.** Two methods were used to estimate the degree of ischemia. The first method determined the mass of myocardium that was ischemic based on several different definitions of ischemia; the second method determined the severity of ischemia based on the myocardial blood flow deficit resulting from each coronary occlusion.

The ischemic tissue mass was determined with the use of a computer program that expressed myocardial blood flow in each sample after coronary occlusion as a percent reduction from blood flow in the appropriate transmural layer of the nonischemic region. Grams of myocardium in which blood flow was reduced greater than 25, 33, 40, 50, and 70% from nonischemic flow were then determined and expressed as percent of LV
weight. Thus, different definitions of the ischemic region were used to include all tissue with a significant reduction in blood flow (>25%), progressing to only tissue with severely reduced flow (>70%).

The myocardial blood flow deficit produced by a coronary occlusion was calculated from the difference between expected and observed total LV myocardial blood flow during ischemia. The expected total myocardial blood flow for each occlusion was estimated by first measuring mean flow in multiple nonischemic tissue samples in each transmural layer. Since previous studies from our laboratory have demonstrated that blood flow in a given epicardial or endocardial layer is comparable in different circumferential regions, nonischemic region blood flow was used to calculate expected flow to the ischemic tissue. Expected blood flow equals the average blood flow to the nonischemic regions times total LV weight. The observed myocardial blood flow equals the sum of flow to all samples in the ischemic region plus total flow to the nonischemic region. The myocardial blood flow deficit was defined by the following formula:

\[
\% \text{ MBF deficit} = \left( \frac{\text{MBF expected} - \text{MBF observed}}{\text{MBF expected}} \right) \times 100 \tag{3}
\]

where MBF equals myocardial blood flow.

Duplicate radioactive microsphere injections were made after 8 coronary occlusions in 4 dogs to determine the reproducibility of measurements of the mass of ischemic myocardium and the myocardial blood flow deficit.

Relation between ejection fraction and blood flow. The relation between the change in ventricular function and extent of acute ischemia following LAD vs. LC coronary occlusion was examined by performing linear regression analyses between the change in EF and the mass of myocardium that was ischemic, using each of the preceding definitions of ischemia or the myocardial blood flow deficit. Slopes and Y intercepts of these linear regression functions were compared by a two-tailed t test. Correlations were also derived using attenuation-corrected EF values.

Multiple linear regression analysis. Changes following coronary occlusion in heart rate, systolic aortic pressure, and LV end-diastolic count rate were calculated as a percent of the control value.

One-way analysis of variance was used to determine differences between dogs with LAD occlusions and those with LC occlusions in multiple anatomic and physiologic variables. Linear regression analysis was performed to examine the relation between the change in global EF and the percent of the left ventricle that was infarcted or ischemic. Multiple linear regression analysis was used to evaluate the relative influence of extent of ischemia and multiple anatomic and hemodynamic variables in determining global EF. The criterion Mallows' \( C^2 \) was applied to all possible subsets regression to select the "best" subset of variables correlating with the change in global EF. The statistical importance of an individual variable is expressed by its contribution to the \( r \) value squared.

Validation of ejection fraction measurements. Additional groups of dogs were prepared with snare-type occluders on the LAD (n = 8) or LC (n = 10) coronary artery and chronic indwelling catheters in the LV chamber, left atrium, and aortic root via the LV apex, atrial appendage, and internal mammary artery, respectively. The occluders were placed at distal or proximal positions to produce a range of ischemic regions. The animals were subjected to permanent coronary occlusions 7–10 days after recovery from surgery. At 3–4 days after occlusions and after ventricular arrhythmia had subsided, EF was measured by both RNA and by biplane contrast left ventriculography. Contrast angiography was performed using a portable C-Arm and video tape recorder. Injections of 20 ml of Renografin-76 were recorded first in the lateral (long axis) and subsequently in the frontal (short axis) projections. A grid was imaged at the level of the midportion of the ventricle in both views. The grid was positioned with the aid of fluoroscopy to assure accurate magnification correction for each view. The videotape data of the angiograms and grids were subsequently digitized using an MDS Spectra imaging system. An effective matrix of 256 × 256 bytes was used. Correction factors (pixels/cm²) were determined from the grid images. Regions of interest were manually drawn using a joystick in both views for systole and diastole. The appropriate magnification correction factor was applied in each view to correct the longest length and area prior to the calculation of volume and EF using the biplane method of Rackley et al.

Results

Table 1 presents summary data for dogs subjected to acute LAD or LC occlusions. The mean anatomic risk regions, expressed as percent of LV weight, were similar in the two groups of animals after distal and proximal coronary occlusion. The larger standard devi-
ations indicate that risk regions were more variable in the LAD animals.

Myocardial blood flow in the 3-mm wide tissue samples taken from immediately outside the margins of the proximal anatomic risk region was 93 ± 19% (mean ± SD) of nonischemic region flow in the epicardial half and 97 ± 15% of nonischemic region flow in the endocardial half after proximal coronary occlusions, indicating that the method used for identification of the risk region included essentially all myocardium that became ischemic after coronary occlusions.

Mean hemodynamic data for LAD and LC animals after distal and proximal occlusions are presented in Table 2. Heart rate increased after proximal, but not distal, occlusions in both groups of animals. Mean ± SD data are given for the control state and for 10 minutes following distal and proximal LAD and LC occlusions.

Reproducibility of Measurements

The EF measurements were highly reproducible over a wide range of values; duplicate measurements differed by 2.3 ± 1.8 (mean ± SD), with r = 0.97. Mean interobserver variability was 1.0 ± 1.2, r = 0.99.

Mean differences between duplicate assessments of the percent of the left ventricle that was ischemic were 1.6 ± 2.8 (>25% reduction in myocardial blood flow), 1.5 ± 2.3 (>33%), 0.9 ± 1.4 (>40%), 1.2 ± 1.4 (>50%), and 0.7 ± 0.9 (>70%). Correlation coefficients for these duplicate measurements ranged from 0.97 to 0.99. The mean variability in myocardial blood flow deficit was 2.2 ± 2.8%, r = 0.95.

Reduction in Ejection Fraction vs. Ischemic Mass

Table 3 lists data from linear regression analyses that relate percent change in EF (y axis) and percent of the left ventricle that was ischemic (x axis) after LAD and LC occlusions. All data points were included that demonstrated a decrease in function and/or ischemia. For each analysis, the ischemic mass was defined by a different quantitative criterion, ranging from only severe reductions in blood flow (>70%) to essentially all myocardium with a significant decrease in blood flow (>25%). Data from 25, 50, and 70% reductions in blood flow are plotted in Figure 1 for the 25 distal or proximal LAD occlusions and in Figure 2 for the 24 LC occlusions. Correlation coefficients ranged from r = 0.84 to 0.90 for LAD occlusions and from r = 0.75 to 0.83 for LC occlusions.

As the criterion for ischemia was varied to include myocardium with >25% to >75% reduction in blood flow, the y intercept progressively increased in both

Table 2. Hemodynamic Data for Dogs With LAD and LC Occlusions

<table>
<thead>
<tr>
<th></th>
<th>LAD occlusions</th>
<th></th>
<th>LC occlusions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Distal</td>
<td>Proximal</td>
<td>Control</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>103 ±15</td>
<td>108 ±17</td>
<td>119 ±27</td>
<td>96 ±16</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
<td>130 ±17</td>
<td>134 ±22</td>
<td>133 ±15</td>
<td>124 ±23</td>
</tr>
<tr>
<td>Diastolic aortic pressure (mm Hg)</td>
<td>91 ±9</td>
<td>91 ±14</td>
<td>94 ±11</td>
<td>81 ±9</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>105 ±14</td>
<td>112 ±16</td>
<td>113 ±13</td>
<td>99 ±12</td>
</tr>
<tr>
<td>Mean LA pressure (mm Hg)</td>
<td>3 ±3</td>
<td>5 ±3</td>
<td>6 ±5</td>
<td>6 ±3</td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LA = left atrium.

Table 3. Correlations Between Reduction in EF and Ischemic Mass

<table>
<thead>
<tr>
<th>Criterion for Ischemia</th>
<th>% Reduction in myocardial blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70</td>
</tr>
<tr>
<td>LAD occlusions</td>
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</tr>
<tr>
<td>r value</td>
<td>0.872</td>
</tr>
<tr>
<td>Y intercept</td>
<td>14.9 ±2.4</td>
</tr>
<tr>
<td>slope</td>
<td>1.22 ±0.14</td>
</tr>
<tr>
<td>LC occlusions</td>
<td></td>
</tr>
<tr>
<td>r value</td>
<td>0.827</td>
</tr>
<tr>
<td>Y intercept</td>
<td>5.9 ±1.9</td>
</tr>
<tr>
<td>slope</td>
<td>0.90 ±0.13</td>
</tr>
</tbody>
</table>

Data are from linear regression analyses performed to compare percent reduction in EF (y axis) with the percent of the left ventricle that was ischemic (x axis). For each analysis, ischemia was defined by a different quantitative criterion. Y intercepts and slopes ± SD are given. For each criterion of ischemia the slope after LC occlusion was less than after LAD occlusion.

* p < 0.005 compared to 70% reduction; p < 0.06 compared to 50% reduction.

† p < 0.025 compared to 70% reduction.
groups of animals (Table 3), indicating that the analyses that excluded milder reduction in blood flow also excluded myocardium that influenced function. In the LAD animals when the ischemic region included only tissue with >70% reduction in blood flow (severe ischemia), >50% reduction in blood flow (moderate and severe ischemia), and >25% reduction in blood flow (mild, moderate, and severe ischemia), the \( Y \) intercepts were 14.9, 9.6, and 1.8, respectively. Thus, the \( Y \) intercepts progressively increased as the criterion for ischemia was increased, indicating progressive exclusion of ischemic myocardium that affected function.

**Figure 1.** Graphs plotting the relation between percent change in left ventricular ejection fraction (EF) and percent of the left ventricle (LV) that was ischemic after 25 acute left anterior descending (LAD) coronary artery occlusions in 13 dogs. Ischemia was defined by a >25% decrease, a >50% decrease, or a >70% decrease in myocardial blood flow compared to nonischemic zone flow. Regression lines and linear correlation coefficients \( r \) for these relations are indicated in the lower right panel. The \( Y \) intercept increased as the criterion for ischemia was increased, indicating progressive exclusion of ischemic myocardium that affected function.

**Figure 2.** Graphs plotting the relation between percent change in EF and percent of the LV that was ischemic after 24 acute left circumflex (LC) coronary artery occlusions in 13 dogs. The format and conclusions are the same as given in the legend for Figure 1.
for ischemia was more restrictive; the regression line approximated a line of identity (slope = 0.96) for the criterion of >25% reduction in blood flow.

In LC animals, the Y intercept increased from 2.0 to 5.9 as the criterion for ischemia became more restrictive (Figure 2). Thus, for both LC occlusions and LAD occlusions, the analyses that included all tissue with a significant (>25%) reduction in blood flow more appropriately considered the mass of ischemic myocardium that affected function.

Slopes of the regression lines ranged from 1.22 to 0.96 for LAD occlusions and from 0.90 to 0.53 for LC occlusions (Table 3). The slopes increased in both groups as the criterion for ischemia became more restrictive, also suggesting that the more restrictive criterion progressively excluded ischemic myocardium that affected function. These data support the conclusion that mild reductions in regional myocardial blood flow affected global LV function; the ischemic region defined by tissue with >25% reduction in flow related best to changes in EF.

The scatter in the graphed data points indicates significant variability in the relation between extent of ischemia and reduction in ventricular function. The basis for this variability is illustrated in Figures 3 (LAD occlusions) and 4 (LC occlusions); measurements after distal and proximal occlusions in individual animals are connected and in general fall on straight lines connecting preocclusion, distal, and proximal points. Two animals fibrillated after proximal LAD occlusion and before a second measurement was made. Two animals with LC occlusions had only one snare. The variability in the linear relation in LAD animals resulted primarily from differences between dogs rather than within a dog; only a few animals increase the variability in the overall relation (Figure 3). In LC animals, there was greater scatter among the dogs; measurements derived from several dogs weakened the relation (Figure 4).

**Figure 3.** Relation between change in EF and extent of ischemia, defined as a >25% decrease in myocardial blood flow after LAD coronary occlusion. The left panel plots all data points. The right panel connects observations from individual dogs: solid lines connect observations from distal to proximal occlusions; dashed lines join measurements made during distal occlusions with the origin, or control state for each study. Data points derived from most of the dogs generally follow a straight line.

**Figure 4.** Relation between change in EF and extent of ischemia, defined as a >25% decrease in myocardial blood flow after LC coronary occlusions. The format is as described in the legend to Figure 3.

**Comparison Between LAD and LC Occlusion**

Using a greater than 25% reduction in blood flow as the criterion for ischemia, the range of ischemic regions after LC occlusions was 0–43% of the left ventricle. The ischemic regions ranged from 0–63% of the left ventricle after LAD occlusion; 4 data points were outside the range of the LC ischemic region.

Linear regression analysis between reduction in EF and ischemic mass demonstrated significantly greater slopes (p<0.01) for LAD than LC occlusions, regardless of the criterion for ischemia (Table 3). Figure 5 illustrates the different slopes using a 25% reduction in blood flow as the definition of ischemia; slopes were 0.96 and 0.53 for LAD and LC occlusion, respectively. Reanalysis of the relation in LAD groups after excluding the 4 data points that are outside the range of the circumflex ischemic regions resulted in r = 0.78, SEE 10.3, and slope = 1.14 compared to r = 0.84, SEE 9.9, and slope = 0.96 for the total LAD group. These data indicate that for comparable degrees of ischemia, LAD occlusions caused greater decreases in EF than LC occlusions.

**Reduction in Ejection Fraction vs. Blood Flow Deficit**

Regression analyses between percent reduction in LV EF and percent total LV myocardial blood flow...
deficit (Figure 6) demonstrated linear relations for both LAD occlusions ($r = 0.89, Y = 1.31X + 2.7$) and LC occlusions ($r = 0.81, Y = 0.83X - 0.1$). As in the previous analyses, the variability in this relation resulted primarily from differences between animals, and the variability was greater after LC occlusions. Linear regression analyses between reduction in EF and blood flow deficit demonstrated significantly greater slopes for LAD than LC occlusions ($p < 0.01$) (Figure 6), indicating greater decreases in EF for comparable degrees of global ischemia. Reanalysis of the LAD group excluding the one data point that was outside the range of ischemia produced by LC occlusion did not significantly change the relationship ($r = 0.88, Y = 1.47X + 0.2$).

**Multiple Linear Regression Analysis**

Table 4 presents results of multiple linear regression analyses performed to examine the relative contribution of LV weight, transmural and subendocardial extent of ischemia, and hemodynamic variables to change in EF following LAD or LC occlusions. Following LAD occlusions the transmural percent LV that was ischemic and the subendocardial percent LV that was ischemic correlated with global EF change with similar coefficients ($r = 0.84$ and $r = 0.79$, respectively). None of the independent variables — LV weight, heart rate change, systolic blood pressure change, or end-diastolic count rate change — correlated significantly with global EF change.

Following LC occlusions, the transmural percent LV that was ischemic and the subendocardial percent LV that was ischemic again correlated with global EF change with similar coefficients ($r = 0.75$ and $r = 0.70$). Both LV weight and heart rate change correlated modestly with global EF change by univariate analysis, but only LV weight contributed significantly ($p = 0.01$) in multivariate analysis.

**Volumetric EF vs. Count EF**

Recalculation of EF from attenuation-corrected volume resulted in slightly higher EF measurements in 16 of 19 comparisons of the LAD occlusions but no consistent effects on EF after LC occlusions. The relation between ischemia and the change in volumetric and count EF following LAD occlusions is presented in Figure 7; the lines derived using volumetric EF are shifted to the right (lower slope and $Y$ intercept) compared to those using count EF. Thus, for any given

<table>
<thead>
<tr>
<th>Table 4. Multivariate Predictors of LV EF Change</th>
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<tbody>
<tr>
<td>LV weight (g)</td>
</tr>
<tr>
<td>LAD occlusions ($n = 25$)</td>
</tr>
<tr>
<td>Univariate $r$</td>
</tr>
<tr>
<td>Multivariate T statistic</td>
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<tr>
<td>2 tail p</td>
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<tr>
<td>Contribution to $r^2$</td>
</tr>
<tr>
<td>$r = 0.836$</td>
</tr>
<tr>
<td>LC occlusions ($n = 24$)</td>
</tr>
<tr>
<td>Univariate $r$</td>
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<tr>
<td>Multivariate T statistic</td>
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<tr>
<td>2 tail p</td>
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<tr>
<td>Contribution to $r^2$</td>
</tr>
<tr>
<td>$r = 0.827$</td>
</tr>
</tbody>
</table>

**Abbreviations:** BP = aortic blood pressure; ED count = background and decay-corrected LV end-diastolic count rate; % LV ischemic-trans = percent of LV myocardium with blood flow reduced >25% relative to nonischemic region flow; % LV ischemic-subendo = percent of reduced LV myocardium with blood flow that was subendocardial (inner 2 of 4 transmural layers).
level of ischemia, there was a smaller change in EF when the attenuation-corrected value was used after LAD occlusion. It is apparent that the heart model that simulated anterior and posterior ischemia with a long axis parallel to the collimator overestimated the effects of LAD and LC ischemia in an intact animal. We observed that the major axis of the LV in the dog was approximately 50–60° relative to the collimator. In addition, larger LAD ischemic regions extended toward the base of the heart and laterally; larger LC ischemic regions extended into the apex regions and laterally. Thus, although the LAD ischemic regions were closer to the collimator than the LC ischemic regions, both occlusions may affect counts near and distal to the collimator.

Validation of EF Measurements

LV EF measured by radionuclide angiography (without correction for attenuation) correlated closely \((r = 0.93, \text{SEE } 5.1)\) with EF calculated by biplane contrast ventriculography following LAD or LC coronary occlusions (Figure 8). The slope was close to the line of identity, and there was no tendency for RNA EF after LAD occlusion to underestimate or LC occlusion to overestimate the contrast angiogram EF.

Discussion

This study describes the quantitative relation between direct measurements of regional myocardial ischemia following acute coronary artery occlusion and changes in global ventricular function as measured by the LV EF. The data support three conclusions concerning this relation that have not been previously addressed in a quantitative fashion in intact, conscious animals: 1) global LV function is very sensitive to mild degrees of acute ischemia; 2) the relation between the degree of acute ischemia and global function is described best by a linear function, and group variability resulted from differences between animals and was greater after LC occlusion; and 3) comparable degrees of ischemia in the LAD distribution as compared to the LC distribution produced greater reductions in global LV function.
Relation of Ischemia to Global Function

Studies\textsuperscript{2-5} have reported quantitative relations between regional myocardial blood flow and regional systolic function measured by ultrasonic dimension crystals; mild reduction (10–30\%) of blood flow resulted in significant segment dysfunction. In the present study, a wide range of ischemic region sizes was produced by subjecting each animal to distal and then proximal coronary artery occlusion. Regional myocardial blood flow was measured by the microsphere technique, which has been shown to be highly reproducible and accurate for assessing myocardial blood flow during myocardial ischemia.\textsuperscript{21,25} Global LV function was assessed by multigated RNA, which has been demonstrated in previous studies to be highly sensitive to changes in global ventricular function as measured by ultrasonic crystals.\textsuperscript{13} Measurements of LV EF by the radionuclide technique were further validated in this study by comparison with EF assessed by biplane contrast ventriculography in dogs following anterior descending or circumflex coronary artery occlusion. Both the blood flow and RNA techniques were demonstrated to be highly reproducible in the present study during myocardial ischemia. In addition, myocardial blood flow measurements recorded immediately outside the region sampled as the ischemic zone were comparable to nonischemic region blood flow, indicating that the postmortem angiographic technique used to identify the margin of the ischemic region adequately separated ischemic and nonischemic myocardium.\textsuperscript{18,19}

The relation between global LV function and acute ischemia was examined in the present study using several different quantitative criteria for characterizing the amount of ischemic myocardium and/or the extent of ischemia. The first analysis related the amount of myocardium with different reductions in blood flow or degrees of ischemia to changes in EF. Although we observed a linear relation between the extent of myocardium that was ischemic and the decrease in EF with each criterion, the relation was best described by including all tissue with \( \geq 25\% \) reduction in blood flow. Restricting the analyses to myocardial tissue with more severe reductions in blood flow progressively excluded myocardium that caused LV dysfunction. These studies indicate that mild degrees of acute blood flow reduction effect significant changes in global LV function. This conclusion is supported by a second analysis of ischemia that utilized calculation of the myocardial blood flow deficit resulting from the occlusion rather than grams of ischemic myocardium. The blood flow deficit considers the severity of ischemia in the entire ischemic region. This analysis was based on previous studies from this laboratory, which have demonstrated that blood flow to circumferential regions within the same transmural layers are essentially the same\textsuperscript{20}; the expected blood flow to the ischemic region was calculated based on blood flow to nonischemic regions. The blood flow deficit was determined as the difference between the expected and measured blood flow to the ischemic region. The relation between ischemic blood flow deficit and the decrease in EF was linear with an intercept close to zero. The slopes of the relation between changes in EF and blood flow deficit were slightly higher than the slopes observed in the previous analysis that defined the ischemic region as grams of myocardium with \( \geq 25\% \) reduction in blood flow.

Regression Relation

The relations between ischemia and changes in global function was best described by linear functions. The group correlations were highest when relating ischemia as a myocardial blood flow deficit to changes in global function; 79 and 65\% of variability in EF was explained by the linear regression relation between change in EF and the blood flow deficit after LAD and LC occlusions, respectively (Figure 6). The linear nature of the response is supported by the response to distal and proximal occlusions in individual dogs (Figures 3 and 4). In most dogs, the data fall on a straight line connecting the preocclusion, distal, and proximal occlusion measurements. The variability in the groups resulted from a few dogs falling on different slopes; variability between dogs was greater after circumflex compared to LAD occlusions. These studies are consistent with the recent report of Akaishi et al\textsuperscript{9} that demonstrated a linear relation between the degree of ischemia and minor axis shortening in acute dogs.

Multivariate analysis demonstrated relatively minor or inconsistent relations between hemodynamic parameters and acute changes in global EF. However, it should be noted that these studies were not designed to assess chronic effects of loading conditions or effects of deliberately altering loading conditions on global EF changes. It is likely that certain of these and other possible unanalyzed variables contributed to the significant scatter in the linear correlations.

Disproportionate Effects of LAD vs. LC Occlusions

Slopes of the regression lines correlating changes in EF with ischemic mass (Figure 5) or with myocardial blood flow deficit (Figure 6) were significantly greater for LAD than for LC occlusions, indicating that for comparable degrees of acute ischemia, LAD compared to LC occlusions resulted in greater decrease in LV function as measured by RNA EF. The disproportionate effects of LAD occlusion were essentially unchanged by excluding 4 data points in Figure 5 and 1 data point in Figure 6 in the LAD group that were outside the ischemic range of the circumflex occlusions.

There are several physiological factors that may contribute to the greater effects of LAD ischemia on global function: 1) myocardial segment shortening in the dog is greater at the LV apex (supplied by the LAD) than at the base (supplied by the LC);\textsuperscript{26} 2) shortening of the LV minor axis, which is largely responsible for generating the stroke volume,\textsuperscript{27} may depend primarily on LAD blood flow; 3) compensatory hypercontraction in normally perfused myocardium may be greater after LC than LAD occlusion;\textsuperscript{24} and 4) epicardial seg-
ment shortening is impaired during acute nontransmural ischemia resulting from LAD stenosis, while epicardial function is preserved until ischemia produced by LC stenosis is transmural.29 Segmental contraction of the anterior compared to the posterior-inferior wall may thus be more sensitive to regional ischemia.

Effects of Attenuation-Correction on RNA EF During Regional Ischemia

In recent studies using a two chamber LV heart model, we observed different effects of simulated anterior vs. posterior hypokinesis on global EF. Anterior hypokinesis resulted in an underestimation of true global EF (lower EF measurements) and posterior hypokinesis resulted in overestimation of true global EF (high EF measurements).15 Disproportionate effects of simulated anterior and posterior hypokinesis on the global EF was corrected by measuring the EF from attenuation-corrected volumes. The heart model was studied as a strict anterior and posterior chamber with the long or major axis of the model parallel to the collimator. In an intact dog or patient, the apex of the heart is closest to the collimator. The major axis of the heart is approximately 50–60° relative to the collimator. The heart model simulated dogs. In addition, larger LC ischemic or infarct regions in the dog extend into the apex area and large LAD ischemic regions extend toward the base of the heart and involve varying amounts of the lateral, as well as anterior, apex. Thus, the heart model simulations overestimated the potential effects of anterior and posterior ischemia on the EF measurements in intact animals. In the present study, the magnitude of the EF correction that resulted from attenuation-corrected volumes was small and did not explain the differential effects of anterior vs. inferior ischemia on EF. The failure of attenuation-correction to explain the disproportionate effects is consistent with the close linear relation (r = 0.93) between EF measured by biplane contrast ventriculography following both LAD and LC occlusions and EF measured by radionuclide angiography without attenuation-correction. The slope was close to the line of identity, and there was no tendency for LAD occlusions to underestimate or LC occlusions to overestimate the contrast EF. These data indicate that the disproportionately greater effect of LAD ischemia on the global EF is due primarily to different pathophysiologic responses to ischemia.

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Relation between myocardial perfusion and left ventricular function following acute coronary occlusion: disproportionate effects of anterior vs. inferior ischemia.

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