Left ventricular ejection fraction after acute coronary occlusion in conscious dogs: relation to the extent and site of myocardial infarction

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ABSTRACT  The change in left ventricular radionuclide ejection fraction after acute occlusion of the left anterior descending (LAD) or circumflex (LC) coronary artery was compared with the ultimate histologic extent of myocardial infarction in conscious dogs. The acute change in ejection fraction correlated with size of infarction in 14 dogs with occlusions of the LAD coronary artery (r = .89, y = 1.12x + 14.2) and in 27 dogs with occlusions of the LC coronary artery (r = .71, y = 0.73x + 7.9); the slope of the regression equation was greater (p < .05) for those with LAD than for those with LC occlusions. Multivariate analysis revealed no independent contribution of left ventricular weight, the subendocardial extent of infarction, or change in heart rate to the acute change in ejection fraction. These data indicate that the decrease in ejection fraction after coronary occlusion is determined primarily by the size of the ischemic area, which also determines size of infarction. In dogs instrumented over a long term, infarcts in the LAD myocardial distribution result in greater decreases in ejection fraction than infarcts of comparable size in the LC distribution.


RESULTS OF A VARIETY of clinical studies support the concept that left ventricular ejection fraction is a measure of ventricular performance that is related to the extent of myocardial infarction.1–5 In conscious dogs linear relationships exist between changes in global and regional ejection fraction measured by radionuclide angiography after acute coronary occlusion and the extent of myocardium with reduced regional blood flow.6,7 Regional myocardial blood flow after coronary occlusion correlates inversely with the extent of histologic necrosis.8,9 Thus, the acute change in ejection fraction would also be expected to correlate with ultimate infarct size.

Previous studies that have examined relationships between measurements of left ventricular performance and extent of infarction1–5 did not consider the influence of anatomic variables such as the location of the infarct and its size relative to the left ventricular weight. The goal of the present study was to assess the relationship between acute changes in ejection fraction after coronary occlusion and direct measurements of the extent of infarction. Studies were performed in awake animals instrumented over the long term to avoid the confounding effects of anesthesia and surgery.

Methods

Experimental animals. Forty-one dogs weighing 20 to 30 kg underwent permanent proximal occlusion of either the left anterior descending (LAD) (14 dogs) or the left circumflex (LC) (27 dogs) coronary artery. They were then maintained for at least 3 days before being killed to permit histologic assessment of infarct size, which was compared with acute changes in radionuclide global and regional ejection fraction.

Surgical preparations. Dogs were anesthetized with sodium thiamylal (30 to 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 secured to the epicardium. A pacing electrode was sutured to the right atrial appendage. All dogs were allowed to recover for 7 to 14 days before being studied.
Experimental protocols. Snare and electrodes were exteriorized from subcutaneous pouches immediately before each study or 1 day earlier. Morphine sulfate, 5 to 10 mg, was injected intravenously before control studies to provide mild sedation and to minimize discomfort resulting from coronary artery occlusion. Dogs were studied awake while lying loosely restrained on their right sides.

Control hemodynamic measurements were made, and radionuclide angiography was performed in duplicate. The snare was then tightened to occlude the artery permanently. Duplicate radionuclide angiograms were acquired 30 to 60 min after occlusion. In the majority of experiments, 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 sinus rate at rest; when occlusion resulted in a sinus rate greater than approximately 120 beats/min, pacing was not performed.

Radionuclide angiography. Multigated equilibrium radionuclide angiography was performed after labeling of red blood cells with 99mTc in vivo. Care was taken to ensure that camera position relative to the thorax remained constant between data acquisitions. Weighted support pads were used to stabilize the chest position.

Global left ventricular ejection fraction was measured in the anterior or ventral projection with slight caudal tilt, a position which provides optimal left ventricular separation from the right ventricle and left atrium.6,10 Global ejection fraction measured in this projection by radionuclide angiography correlates closely with that obtained simultaneously with use of ultrasonic dimension crystals over a wide range of ventricular function.10 Regional ejection fraction was determined in both the anterior and 60 degree left anterior oblique projections with the use of a computer program that divided the left ventricle into quadrants with a nongeometric or count-based center (figure 1).6 After both LAD and LC coronary artery occlusions, the magnitude of change in regional ejection fraction is significantly greater than the magnitude of change in global ejection fraction, although the quadrants analyzed do not assess left ventricular function in anatomically or physiologically discrete myocardial zones.6 The mean difference (± SD) between duplicate measurements of global ejection fraction in conscious dogs is 0.02 ± 0.02; the mean difference between global ejection fraction determined by different observers is 0.01 ± 0.01.6 The mean difference between duplicate measurements of regional ejection fraction ranges from 0.03 ± 0.02 to 0.04 ± 0.04; the mean interobserver variability in these values is 0.02 ± 0.02 to 0.05 ± 0.04.6

Quantitation of infarction. Dogs were killed a minimum of 3 days after coronary occlusion to allow sharp separation of infarcted and noninfarcted myocardium by routine histologic techniques.8,9 The hearts were excised and placed in buffered formalin for 3 days to permit fixation. The left ventricle was sliced into four transverse rings from base to apex. The basal and apical rings were cut into four circumferential regions: anterior, septal, posterior, and lateral. The two middle rings were cut into six circumferential regions: anterior, septal, posterior, papillary muscle, lateral, and anterior papillary muscle. Each circumferential region was cut into four transmural samples from subepicardium to subendocardium, each weighing 1 to 2 g. The tissue samples were weighed, embedded in paraffin, sectioned at two different depths, and stained with hematoxylin and eosin.5,9 The samples were arranged so that each histologic section demonstrated the transmural distribution of infarction in the region. Infarcted myocardium was sharply distinguished from intact myocardium and was characterized by complete or partial cellular dissolution, inflammatory cell infiltration, and loss of normal cell architecture. Sketches of the histologic extent of infarcted and of uninvolved myocardium in each tissue sample were then quantitated by planimetry with a graph pen ultrasonic digitizer and computer interface.8,9 Total weight of the infarcted tissue was calculated as the sum of weights of infarcted tissue in each individual sample. The weight of infarcted tissue in the subendocardial half of the myocardial wall was determined. Infarct weight was expressed as a percentage of left ventricular weight.

Data analysis. The average of duplicate measurements of global and regional ejection fraction was used in the analysis. The left ventricular region manifesting the maximum change in regional ejection fraction after acute coronary occlusion was identified for each dog.6 The absolute acute decrease in ejection fraction was divided by the control value, and expressed as a percent of control. Similarly, the acute change in heart rate was calculated as a percent decrease from control.

One-way analysis of variance was used to determine differences between dogs with LAD and those with LC coronary artery occlusions with respect to multiple anatomic and physiologic variables. Linear regression analysis was performed to examine the relationship between the change in global ejection fraction and the percent of the left ventricle that was infarcted. Multiple linear regression analysis was used to evaluate the relative influence of the extent of infarction, the subendocardial extent of infarction, the left ventricular weight, and the change in heart rate in determining global ejection fraction. The criterion Mallows' Cp11 was applied to all possible subsets regression12 to select the “best” subset of variables correlating with the change in global ejection fraction. The statistical importance of an individual variable is expressed by its contribution to the r value squared.

Results

Table 1 presents mean left ventricular weights, histologic infarct sizes, and heart rate and radionuclide angiographic data for dogs subjected to LAD or LC coronary artery occlusions. Mean left ventricular weight and percent of left ventricle infarcted did not differ between groups. Mean heart rate was greater at control and after occlusion in the LAD group, but

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<table>
<thead>
<tr>
<th>Dog No.</th>
<th>LAD artery occlusion</th>
<th>LC artery occlusion</th>
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<td>% LV Infarcted</td>
<td>Heart rate (bpm)</td>
<td>Global EF</td>
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EF = ejection fraction; LV = left ventricle.
<sup>a</sup>Region demonstrating the maximum acute decrease in EF following coronary occlusion.
p values reflect results of analysis of variance comparing LAD occlusions to LC occlusions. For heart rate, global EF and regional EF, percent change from control to occlusion was compared in the two groups.
increased to a similar extent (p = .11) in both groups. Mean global and regional ejection fractions were lower in the control state and after occlusion in the LAD group. Percent change in global ejection fraction was greater (p = .03) in dogs with LAD coronary artery occlusion than in those with occlusion of the LC artery (34.2 ± 19.7 vs 20.7 ± 13.1, mean ± SD). Changes in regional ejection fraction were greater than those in global ejection fraction after both LAD and LC artery occlusions; however, the percent change in regional ejection fraction did not differ significantly (p = .13) between groups (45.6 ± 23.1 vs 34.9 ± 14.2).

In figure 2 the percent change in global ejection fraction measured within 1 hr after occlusion of the LAD or LC coronary artery is plotted against the percent of the left ventricle that ultimately infarcted. After LAD artery occlusion, histologic infarct size ranged from 0 to 51.7% of the left ventricular weight and correlated linearly (r = .89) with percent change in global ejection fraction (y = 1.12x + 14.2). After occlusion of the LC artery, infarct size ranged from 1.4% to 36.9% of the left ventricular weight and correlated modestly (r = .71) with change in ejection fraction (y = 0.73x + 7.9). The slope of this relationship was significantly greater (p < .05) for dogs with LAD (1.12) than for those with LC (0.73) artery occlusions, indicating that for comparable ultimate infarct size, acute LAD artery occlusion decreased global ejection fraction to a greater degree than did acute LC artery occlusion. In addition, y axis intercepts were significantly greater than 0 after occlusion of both the LAD (p < .003) and LC (p < .02) arteries, suggesting that after acute coronary occlusion, the reduction in global ejection fraction was influenced by dysfunction in myocardium that did not become irreversibly injured.

Multivariate analysis revealed that the left ventricular weight and the subendocardial extent of infarction did not independently influence the change in ejection fraction after coronary occlusion. After occlusion of the LC, but not after that of the LAD, there was a modest inverse correlation between the change in heart rate and the change in global ejection fraction (r = −.49): that is, increases in heart rate were associated with decreases in ejection fraction. Neither the control value for global ejection fraction, regional ejection fraction, nor heart rate influenced the change in global ejection fraction after coronary occlusion in either group. Thus, although there were baseline differences between the LAD and LC groups with respect to heart rate and global ejection fraction (table 1), these variables were not independently predictive of the change in ejection fraction after occlusion.

**Discussion**

The major new findings of the present study are that (1) the acute reduction in global ejection fraction that follows coronary artery occlusion is directly related to the extent of final myocardial infarction, and (2) infarction occurring in the LAD as compared with the LC region of the dog left ventricle results in dispropor-

![FIGURE 2. Relationships between percent change in global ejection fraction and percent of the left ventricle that infarcted after LAD (left) and LC (right) artery occlusions. The slope was significantly greater (p < .05) for the LAD than for the LC group. The y intercepts were significantly greater than 0 for both LAD (p < .003) and LC (p < .02) artery occlusions.](http://circ.ahajournals.org)
tionately greater reduction in global left ventricular function as measured by the radionuclide angiographic
technique.

Occlusion of the LAD or LC artery produced a wide range of infarct sizes. The variability resulted in part from
the modification of the site of occlusion and in part from inherent variability in the extent of ischemia and
subsequent infarction resulting from proximal coronary occlusion in conscious dogs. The entire left ventricle was
sectioned into 1 to 2 g samples for direct histologic quantitation of size of infarction. In previous studies of acute coronary occlusion we used similar techniques for tissue sectioning, but analyzed regional myocardial blood flow rather than histologic infarction. In the earlier experiments the size of the ischemic zone was estimated as the percent of the left ventricular weight in which myocardial blood flow was reduced more than 25% from normal zone flow. The acute change in global ejection fraction correlated with size of the ischemic zone in 13 dogs with LAD artery occlusions (r = .84, y = 0.96x + 1.7) and in 13 dogs with occlusions of the LC artery (r = .75, y = 0.53x + 2.0).

It is of interest that the slopes of the relationships between decrease in ejection fraction and infarct size tended to be greater than the slopes of the relationships between decrease in ejection fraction and extent of ischemia for both LAD (1.12 vs 0.96) and LC artery occlusions (0.73 vs 0.53). The y axis (change in ejection fraction) intercepts were greater than 0 for the relationships of infarct size to change in ejection fraction, whereas the y intercepts were close to 0 for the relationships of the extent of ischemia to change in ejection fraction. These data indicate that the global ejection fraction is sensitive to mild reductions in regional blood flow; consequently, acute reductions in global ejection fraction are influenced both by the amount of myocardium that infarcts and by the amount that does not infarct after permanent coronary occlusion. It is not surprising that both the extent of acute ischemia after coronary occlusion and the extent of subsequent infarction are directly related to the changes in global ejection fraction, since several studies have demonstrated direct relationships between myocardial ischemia and infarction.

Multivariate analysis demonstrated no consistent relationships between left ventricular weight, the subendocardial extent of infarction, or the change in heart rate and acute changes in global ejection fraction. In our previous examination of the relationship between the size of the ischemic zone and the change in ejection fraction, a more extensive analysis was performed to assess the influence of acute changes in heart rate, aortic blood pressure, and the left ventricular end-diastolic count rate, a radionuclide index of relative left ventricular volume. None of these variables correlated independently with the change in ejection fraction. However, it should be noted that neither the present protocol nor the previous one was designed to assess long-term effects of loading conditions or effects of deliberately altering loading conditions on changes in global ejection fraction. It is likely that certain of these and other unanalyzed variables contributed to the significant scatter in the linear correlations.

A significant finding of this study was that for similar degrees of left ventricular infarction, occlusion of the LAD artery produced greater decreases in global ejection fraction than did occlusion of the LC artery. It is of interest that the decreases in regional ejection fraction after the two occlusions were not significantly different, suggesting that the disproportionate effects of LAD vs LC regional ischemia on left ventricular function were more apparent at a global than at a regional level. Our previous work has indicated a modest linear relationship between acute decreases in regional ejection fraction and size of the ischemic zone after occlusion of both the LAD and LC. This makes it unlikely that the radionuclide angiographic technique preferentially evaluated regional function in dogs that had LAD vs LC artery occlusions in the present study. The present findings with regard to global function are consistent with observations made in experiments in which size of the ischemic zone rather than size of infarction was estimated. In the earlier study the slope of the relationship between the change in global ejection fraction and size of the ischemic zone was also greater for LAD than for LC artery occlusions (0.96 vs 0.53; p < .01). While global ejection fraction decreased to a greater extent after LAD than after LC artery occlusions (27.7% vs 13.4%; p = .004), regional ejection fraction decreased to a similar extent in the two groups.

The mechanisms or factors responsible for the disproportionate effects of LAD vs LC artery occlusion on global function are not clear. The anatomic distributions of infarction or ischemia were different with occlusion of the LAD artery than with that of the LC, and consequently may have influenced global ejection fraction in different ways. Occlusion of the LAD coronary artery induced infarction of the anterior-apical region, with variable extension toward the base, whereas occlusion of the LC artery induced infarction of the inferior-basal region, with variable extension.
toward the apex. Larger LAD artery infarcts tended to involve more of the anterior and lateral walls and extended toward the base, whereas larger LC artery infarcts tended to extend more medially and laterally than toward the apex. It has not been determined in studies in the dog to what extent LAD as compared with LC artery occlusions preferentially affect minor- or major-axis shortening, although as noted above the larger infarcts with LC artery occlusion may be expected to involve shortening in both the major and minor axes. Previous investigations have indicated that myocardial segment shortening in the dog is greater at the apex than at the base of the left ventricle, and infarction of a left ventricular region that shortens to a greater degree than the remainder of the ventricle may be expected to alter global function disproportionately. On the other hand, shortening of the left ventricular minor axis contributes approximately 87% to generation of the stroke volume.

Studies have suggested that hypofunction may extend for a variable distance outside the ischemic zone, possibly as a result of tethering. It is not known whether the adjacent hypofunctional nonischemic region influences global function or whether the hypofunctional nonischemic region is larger after LAD than after LC artery occlusion. Global left ventricular contraction represents the sum of shortening in the nonischemic and ischemic regions. Although the present studies indicate that hyperfunction in the nonischemic region rarely compensates completely for acute ischemic region hypofunction, in certain studies it has been observed that there is less hypercontraction in nonischemic myocardium remote from the ischemic region after LAD than after LC occlusion in the dog. Such a regional difference would contribute to disproportionate effects of LAD and LC artery occlusion on global ejection fraction.

Finally, in phantom heart studies performed to simulate results of radionuclide angiography during regional left ventricular dysfunction, there was greater attenuation of counts from hypofunctional regions that were distant from the detector and consequently true volume changes from simulated posterior and anterior hypokinesis were underestimated and overestimated, respectively. This theoretical problem, however, had only a minor effect on measurements of ejection fraction in experiments in conscious dogs. It is of interest that in several clinical studies it has been observed that anterior infarction causes greater decreases in left ventricular function than does inferior infarction, but it is not clear from these studies whether the differential effects on global function resulted from different sizes of infarction or different physiologic effects of infarcts of comparable size.

This study demonstrates a major influence of the extent of acute infarction on changes in left ventricular ejection fraction and relatively minor influences of other parameters. The results presented are consistent with those of an earlier experiment in which the size of the ischemic zone was correlated with acute changes in ejection fraction. In both studies anterior ischemia produced greater reduction in global ejection fraction than did inferior ischemia of a similar extent. Although the precise mechanisms responsible for this disproportionate effect have not been determined, the observation is pertinent to the angiographic evaluation of global function in the setting of acute infarction.

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References
12. Frane JW: All possible subsets regression. In Dixon WJ, editor:
BMDP statistical software. Los Angeles, 1981, University of Calif
Press. p 264
13. LeWinter MM, Kent RS, Krowner JM, Carew TE, Covell JW:
Regional differences in myocardial performance in the left ventri-
14. Rankin JS, McHale PA, Arentzen CF, Ling O, Greenfield JC Jr,
Anderson RW: The three-dimensional dynamic geometry of the left
15. Sakai K, Watanobe K, Millard RW: The extent of hypokinetic
function surrounding focal transmural ischemia. Circulation
68(suppl III): 111-194, 1983 (abst)
16. Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner
SF: Regional myocardial functional and electrophysical alterations
after brief coronary artery occlusion in conscious dogs. J Clin
Invest 56: 978, 1975
S: Regional myocardial function and dimensions early and late
after myocardial infarction in the unanesthetized dog. Circ Res 40:
158, 1977
18. Schneider RM, Jaszczak RJ, Coleman RE, Cobb FR: Dispropor-
tionate effects of regional hypokinesis on radionuclide ejection
fraction: Compensation using attenuation-corrected ventricular
effects of anterior versus inferior ischemia on global radionuclide
ejection fraction: effects of photon attenuation. Circulation
68(suppl III): III-207, 1983
20. Russell RO Jr, Hunt D, Rackley CE: Left ventricular hemodynam-
ics in anterior and inferior myocardial infarction. Am J Cardiol 32:
8, 1973
Padmanabhan VS: Clinical, hemodynamic and angiographic aspects
of inferior and anterior myocardial infarctions in patients with
angina pectoris. Am J Cardiol 34: 513, 1974
22. Miller RR, Olson HG, Vismara LA, Bogren HG, Amsterdam EA,
Mason DT: Pump dysfunction after myocardial infarction: import-
tance of location, extent and pattern of abnormal left ventricular
Left ventricular ejection fraction after acute coronary occlusion in conscious dogs: relation to the extent and site of myocardial infarction.
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