Effect of Extension of Infarction on Serial CK Activity

FREDERICK R. COBB, M.D., ROBERT G. IRVIN, M.D., RICHARD C. HAGERTY, M.D., AND CHARLES C. ROE, M.D.

SUMMARY The effects of extension of myocardial infarction produced by reduction of regional myocardial blood flow (RMBF) to an ischemic region on serum CK activity were examined in 14 awake dogs. Initial infarction was effected by occlusion of the distal left circumflex coronary artery (LCCA) and subsequent extension was produced by occlusion of the proximal LCCA 6, 12 or 18 hours after distal occlusion. Extension was verified by serial measurements of RMBF using radioisotope-labeled microspheres before and after proximal occlusion.

Serum CK activity increased initially 2–4 hours after distal coronary occlusion and then increased rapidly and reached peak values 12 hours after occlusion. When the infarction was extended at 6, 12 or 18 hours after the initial occlusion, CK appearance was immediately reduced in the 6- and 12-hour experiments, but not in the 18-hour experiments. Extension of infarction at each interval caused delayed increases in CK activity beginning 2–5 hours after proximal occlusion, with peak values occurring 12 hours later. The immediate effects of extension of infarction by reducing blood flow on CK activity are a function of whether the infarcted myocardium continued to release CK, e.g., at 6 and 12 hours after occlusion, or CK release was completed, e.g., 18 hours. The immediate effects of extension of infarction were the result of perfusion on myocardium that is infarcted and continues to release CK, and do not necessarily indicate alterations in the extent of myocardial injury. The delayed effects of proximal and distal occlusion on CK activity were comparable, suggesting that delayed and not immediate alterations in CK activity represent extension of infarction.

ELEVATION of serum creatine kinase (CK) and the presence of the MB isoenzyme in the blood have proven to be highly sensitive and specific indices of acute myocardial infarction.9-8 In addition, certain changes in CK levels during serial measurements of enzymes have been interpreted as evidence of alterations in the extent of myocardial infarction.4-8 Increases in serum CK levels coincident with initiation of certain interventions have been interpreted as extension of infarction.6, 7 While decreases in CK levels have been interpreted as reduction in the extent of injury.6, 8 Other studies have indicated that an important determinant of CK appearance may be blood flow to the acute injured region.8-11 Restoration of blood flow to an acutely injured area causes an immediate increase in CK appearance.9, 10 The finding of relatively less CK appearance in the blood after large compared with smaller infarcts may be secondary to greater ischemia during the interval of CK release in the larger infarcts.11, 12 These studies suggest that interventions that extend infarction by reducing blood flow may reduce CK appearance.

In this study we examined the effects of infarct extension on serum CK activity produced by reduction of blood flow to regions that contain ischemic myocardium at various intervals after initiation of infarction. Acute myocardial infarction and subsequent extension of infarction were effected by occlusion of the distal and proximal circumflex coronary artery, respectively. Extension of infarction was verified by serial measurements of regional myocardial blood flow to regions containing ischemic tissue. Studies were carried out in awake, chronically instrumented dogs to avoid variables of anesthesia and surgery.

Methods

Animal Preparations

Fourteen mongrel dogs weighing 20–30 kg were anesthetized with thiamylal sodium (30–40 mg/kg) and underwent a left thoracotomy. Two adjustable snare occluders were positioned on the left circumflex coronary artery in each dog. One snare was positioned distal and the other proximal to the first large marginal branch. Heparin-filled catheters were inserted into the left atrial cavity and the aortic root. The catheters were tunneled to a subcutaneous pouch at the base of the neck and the snares were tunneled to a lateral subcutaneous pouch. Studies were performed 6–9 days after surgery. On the morning of the study, the snares and catheters were brought to the exterior while the dog was anesthetized with subcutaneous lidocaine infiltration. The dogs were loosely restrained and studied while awake and resting quietly on the right side. Aortic and left atrial pressure catheters were attached to pressure transducers (Statham Model P23Db). A lead III ECG and phasic and mean pressure were recorded on a direct writing oscillograph (Hewlett-Packard Model 8800) and an eight-channel magnetic tape recorder (Hewlett-
Packard Model 3917-A). After all recording instruments had been connected, a 30–45-minute period was allowed for the dogs to adjust to the quiet laboratory conditions. Acute myocardial infarction was then produced by complete closure of the snare on the distal circumflex coronary artery. Morphine sulfate, 10 mg, was administered intravenously in 2–3 mg dosages during the first 30 minutes after occlusion to minimize any discomfort resulting from the occlusion. Lidocaine, 2 mg/kg was administered as a bolus injection at 15-minute intervals for the first hour. No analgesics or antiarrhythmic agents were administered after the initial 1 hour of occlusion. Intramuscular injections were not used. Three dogs developed ventricular fibrillation after distal occlusion and were excluded from the study. None of the dogs included in the study were subjected to DC cardioversion. Extension of infarction was produced by occlusion of the snare on the proximal circumflex coronary artery 6, 12 or 18 hours after distal occlusion.

Venous blood samples were obtained at 1–2-hour intervals after the distal occlusion, at 15–30-minute intervals for 2 hours after the proximal occlusion and at 2-hour intervals for 24 hours after the initial occlusion. Blood samples were then obtained at approximately 4-hour intervals for a total of 60–72 hours after the initial occlusion.

**Regional Myocardial Blood Flow**

Regional myocardial blood flow was measured serially using carbonized microspheres, 7–10 µ in diameter, labeled with gamma-emitting nuclides, ⁶¹⁴Cr, ¹¹⁴⁴Ce, ⁸⁵⁴Sr, and ⁶⁶⁴Sc, as described in previous studies.¹³⁻¹⁵ Regional blood flow was measured 2 hours after distal occlusion, immediately before and 2 hours after proximal occlusion and 24 hours after the initial occlusion.

Five days after coronary occlusion the dogs were sacrificed and the hearts placed in 10% buffered formalin for 4–6 days. As shown in figure 1, the left ventricle was sectioned into four transverse sections, multiple circumferential regions, and finally into four transmural layers of approximately equal thickness (sample size 1–2 g). Ten percent buffered formalin was added to the counting vials to preserve the tissue for histologic section after measurement of the tissue radioactivity.

The radioactivity in each myocardial sample and reference blood sample was determined in a gamma spectrometer, using window settings selected to correspond to peak energies of each radioactive nuclide. Blood flow to each myocardial sample in ml/min/g was calculated using the formula:

\[
Q_m = Q_r \times C_m/C_r
\]

where \(Q_m\) = myocardial blood flow (ml/min); \(Q_r\) = reference flow (ml/min); \(C_m\) = counts/min in myocardial samples; and \(C_r\) = counts/min in reference flow sample.

**Histologic Measurements of Infarction**

After measuring tissue radioactivity and calculating blood flow to each myocardial sample, the samples were prepared for histologic sectioning by recombining the segments from each circumferential region in the pre-cut transmural sequence.¹³⁻¹⁵ Four-step histologic sections were obtained from each tissue block containing the four transmural sections. The sections were stained with hematoxylin and eosin. Myocardial infarction was defined as complete or partial cellular dissolution, inflammatory cell infiltrate, and loss of normal cellular architecture. Sketches were made of the intact and infarcted myocardium in each tissue section using a projection microscope. The percentage of myocardial infarction in each sample was determined by planimetry using a sonic X-Y digitizer (Graf-Pen) interfaced to an IBM digital computer programmed to calculate areas. Thus, regional blood flow and the extent of myocardial infarction were determined in multiple small tissue samples of the entire region subjected to ischemia. Total infarct weight was determined from the sum of the weights of infarction in each tissue sample.
Estimates of Infarction from Enzyme Measurements

Serial serum CK measurements were performed using a modified Rosalki reagent\textsuperscript{18} (Spinchem, Smith-Kline Instruments) at 37°C and a Centrifichem programmable centrifugal analyzer (Union Carbide Corp.). Triplcate assays were performed on each serum sample and a mean value for each sample expressed as units per liter was used. The precision of the measurements remained within 3 millioptical density units for each determination.

Electrophoresis\textsuperscript{17} of each sample was performed to estimate the extent of noncardiac contribution to CK levels that might produce overestimation of infarct size based on serial CK activity measurements. The estimation of infarct size was carried out using serial CK measurements. An individualized $K_d$ was not used in the present analysis,\textsuperscript{19} since previous studies have shown\textsuperscript{12, 20} that an individualized $K_a$ did not result in closer relationship between CK estimates and direct measurements of infarction. The originally recommended parameters\textsuperscript{18} were used in the present study.\textsuperscript{12} The value for $K_a$ was $-0.0045 \text{ min}^{-1}$. The values for $K_w$, the proportion of body weight in which the enzyme was distributed, was 0.114. The value for $K_e$, the ratio of total enzyme appearance in the blood to total CK disappearance from infarcted myocardium, was 0.30. The value for $K_{ep}$, the amount of enzyme depleted per gram of infarcted myocardium, was 1366 IU. The $K_D$ value was adjusted for temperature at 37°C.\textsuperscript{12} Use of different values\textsuperscript{21} for the constants in the formula has not been found to alter the relationships between CK estimates and direct measurements of infarction.\textsuperscript{12}

Results

Hemodynamic Measurements

Mean hemodynamic measurements are shown in table 1. Occlusion of the distal circumflex coronary artery resulted in significant increases in heart rate and arterial and left atrial pressure. Before extension, heart rate was increased and arterial and left atrial pressure were not significantly different from control values. Extension of infarction resulted in significant increases in left atrial pressure, but no change in heart rate or arterial pressure.

Extension of Infarction at 18 Hours

Five dogs were subjected to infarct extension by occlusion of the proximal circumflex coronary artery 18 hours after distal occlusion (fig. 2). CK activity began to increase 2–4 hours after initial distal occlusion and reached peak CK activity approximately 12 hours (9, 12, 12, 12 and 15 hours) later.

Extension of infarction by proximal coronary occlusion at 18 hours occurred when CK activity had been decreasing for several hours in each dog. After proximal occlusion, CK activity continued to decrease for 2–5 hours before increasing to reach a second peak value 9–14.5 hours later. Extension of infarction at this interval had no immediate effect on serum CK activity that could be differentiated from the rate of endogenous CK clearance. The intervals from occlusion to initial increase and peak values of CK activity were comparable after the initial occlusion and extension at 18 hours.

Regional blood flow values in transmural layers from the regions perfused by the circumflex coronary artery, i.e., posterior, posterior papillary and lateral regions, were averaged in each dog and are plotted in figures 3, 4, and 5. Samples from ring 4, the apex ring, were not included unless infarction was present; infarction occurred in the posterior segment of ring 4 in three dogs. In each dog both distal and proximal coronary occlusion reduced blood flow to the regions containing ischemic myocardium (fig. 3). In individual dogs there was a general relationship between the degree of blood flow reduction and the magnitude of the subsequent CK curves. For example, in dogs 1 and 5, compared with the other dogs, distal (initial) occlusion decreased regional myocardial blood flow relatively less than proximal (extension) occlusion and caused a relatively smaller CK curve. In dog 1, compared with dog 5, proximal rather than distal occlusion reduced blood flow less and resulted in a smaller subsequent CK curve. In dog 4, which had a large initial and small secondary CK curve, distal occlusion markedly decreased blood flow to the posterior papillary region, while proximal occlusion decreased blood flow only in the lateral region, i.e., from 0.63 to 0.38 ml/min/g. The relationship between reduction in blood flow and CK appearance did not hold when measurements between dogs were compared. For example, the largest CK curve occurred in dog 5 after proximal occlusion, although the reduction in blood flow was greater in dogs 2 and 3. Twenty-four hours after occlusion in dog 5, regional myocardial blood flow had increased markedly to each region of the ischemic zone, while in dogs 2 and 3 blood flow had increased much less. These data suggest that CK appearance is a function of both the severity of the ischemia, which determines the extent of tissue necrosis, and subsequent changes in blood flow to the regions containing infarcted myocardium.

Extension of Infarction at 12 Hours

Five dogs were subjected to infarct extension by occlusion of the proximal left circumflex coronary artery 12 hours after distal occlusion (fig. 6). Thus, the second occlusion was applied at approximately the peak of the initial enzyme curve. In each dog, CK levels decreased immediately after the proximal occlusion. In each dog, CK activity continued to decrease for a minimum of 3 hours (range 3–5.5 hours) before increasing. Secondary peaks were reached between 8–13.5 hours after the proximal (extension) occlusion, or 20–25 hours after the distal (initial) occlusion. The intervals from distal and proximal occlusion to initial increases and peak values of CK activity were com-
parable. Dog 3 died suddenly as a result of ventricular fibrillation 23 hours after the initial occlusion; the second enzyme peak had been reached, but the total enzyme curve had not been completed.

In each dog, proximal occlusion decreased regional myocardial blood flow in the posterior papillary and lateral regions (fig. 4). As with the previous group, there was a general relationship between the magnitude of the reduction of flow and the magnitude of the subsequent CK curves in individual dogs. In dog 1, proximal occlusion markedly decreased regional myocardial blood flow in all three regions containing ischemic tissue and resulted in a CK curve that was relatively greater than the initial curve. In dog 2, which had a large initial and relatively smaller second CK curve, regional myocardial blood flow decreased markedly in all regions containing ischemic myocardium after the distal occlusion, but decreased relatively less after the proximal occlusion. The relationship between the magnitude of the flow reduction and CK curves did not hold for every experiment. For example, in dog 5, compared with the remaining dogs, the initial decrease in regional myocardial blood flow was relatively less, but the peak CK value exceeded the values in the remaining dogs. The large secondary peak in this dog, however, was related to reductions in flow in all three regions.

**Extension of Infarction at 6 Hours**

Four dogs were subjected to infarct extension by proximal occlusion of the left circumflex coronary artery 6 hours after occlusion of the distal snare (fig. 7). As in the previous groups, increases in serum CK activity were detected 2–4 hours after occlusion. In contrast to the findings in dogs with infarct extension produced at 12 and 18 hours after infarction, secondary occlusion 6 hours after distal occlusion delayed the time to reach peak CK values by approximately 6 hours in dogs 1, 2 and 3, markedly decreased the rate

| Table 1. Hemodynamic Measurements Before and After Coronary Artery Occlusion |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Before occlusion | 2 Hours | Before extension | After extension | 24 Hours |
| HR (beats/min)  | 85 ± 16         | 107 ± 26 | 151 ± 46        | 151 ± 42        | 151 ± 23  |
| p                | 0.01            | <0.01   | <0.01           | <0.01           | <0.01    |
| AP (mm Hg)      | 96 ± 12         | 112 ± 13 | 92 ± 13        | 98 ± 16        | 82 ± 9   |
| p                | <0.01           | NS      | NS              | <0.01           | <0.01    |
| LAP (mm Hg)     | 4.6 ± 2.0       | 7.1 ± 3.3 | 4.4 ± 2.3     | 6.5 ± 3.4     | 4.8 ± 2.0 |
| p                | 0.01            | NS      | 0.05            | NS              |          |

*p* values compare mean values to control measurements. NS = *p* > 0.05.

Abbreviations: HR = heart rate; AP = arterial pressure; LAP = left atrial pressure.
of CK appearance in dogs 1 and 2, but caused no detectable change in CK appearance or time to reach peak CK values in dog 4. In dogs 1 and 2, CK values remained on a plateau for 2–3 hours after the second occlusion and then rapidly increased to reach peak values 10–12 hours after the proximal occlusion, 16–18 hours after the initial occlusion.

Proximal occlusion of the circumflex coronary artery 6 hours after distal occlusion in dogs 1, 2 and 3 reduced blood flow markedly to the posterior papillary and lateral regions (fig. 7). The slight alterations in regional myocardial blood flow in dog 4 caused by the same procedure (blood flow to the lateral segments decreased from 0.81 to 0.58 ml/min/g of tissue) were not sufficient to produce detectable changes in the serum CK appearance.

Relationship Between CK Estimates and Histologic Measurements of Infarction

The relationship between CK estimates and histologic infarction is plotted in figure 8. Histologic infarction ranged from 4.1–56.1 g, or 3–44% of the left ventricular mass. There was a poor correlation between CK estimates and histologic infarction, $r^2 = 0.13$, in the total group of dogs. Previous studies using this model have demonstrated a similar poor relationship over a wide range of infarction sizes, but a good relationship when only smaller infarcts were analyzed. Only three dogs in this study sustained histologic infarctions of less than 20 g, and regression analysis was inappropriate. However, in these three dogs, CK estimates increased as histologic size increased. As histologic infarct size exceeded 20 g, CK estimates of infarction were variable and in general were relatively less than estimates determined in the smaller infarcts. Noncardiac CK-BB contributed an average of 12.7% ± 1.7 (SEM) to the total CK estimate of infarct size. The relationship between CK estimates and histology was not improved by subtracting noncardiac BB isoenzyme values from the total CK values, using individualized $k_d$, or using other recommended parameter values: Each adjustment yielded an $r^2$ of 0.15 or less.
Discussion

The objective of the present study was to measure changes in serum CK during the course of acute myocardial infarction complicated by extension of infarction. The characterization of these alterations should provide some understanding of how well serial serum enzymes may reflect extension of infarction resulting from reduction in blood flow to regions containing ischemic myocardium. The experimental protocol produced varying reductions in blood flow to the regions containing ischemic myocardium after distal and proximal occlusions because the size of the first marginal branch of the circumflex artery varies from dog to dog.

Significant increases in serum CK occurred 2–4 hours after coronary occlusion. After initial increases, CK values increased rapidly and reached peak values approximately 12 hours after the initial occlusion. Shell et al. observed similar intervals from occlusion to initial increases and peak CK values after left anterior descending coronary artery occlusion. Thus, extension of infarction at 6, 12, and 18 hours after initiation of infarction occurred during the period of rapidly increasing CK activity, at peak CK activity, and after approximately 6 hours of decreasing CK activity, respectively. Extension of infarction resulted in immediate alterations in serum CK activity, which varied as a function of the time from the initial occlusion and delayed alterations in CK activity, which were comparable in each group. Extension of infarction at 6 hours effected immediate decreases in the rate of CK appearance and prolonged the time from the initial occlusion to peak CK activity; peak CK activity occurred 12 hours after extension or 18 hours after the initial occlusion. Extension of infarction 12 hours after the initial occlusion resulted in immediate decreases in CK activity; CK activity continued to decrease for at least 3 hours before increasing to reach secondary peak values approximately 12 hours after extension. Extension of infarction 18 hours after initial occlusion had no immediate effect on CK activity that could be differentiated from endogenous clearance; CK levels continued to decrease for 2–5 hours before increasing to reach secondary peak levels approximately 12 hours after extension.

Interpretation of changes in blood flow to the ischemic region is complicated by the fact that the posterior, posterior papillary and lateral regions probably contained a mixture of ischemic and non-ischemic myocardium after distal occlusion. Decreases in blood flow in these regions as a result of proximal occlusion may represent reduction in flow to the nonischemic and/or ischemic myocardium in the sample. Since reduction in blood flow altered CK appearance at 6 and 12 hours after occlusion, a portion of the reduced flow may have occurred in the areas that were releasing CK, e.g., the original ischemic zone. Alternatively, reductions in blood flow to nonischemic myocardium adjacent to the original ischemic zone may have secondarily delayed CK release from the original ischemic zone. Since the sample size was approximately 1–2 g, the reductions in flow in response to proximal occlusion occurred in regions in close proximity to, if not in, the original ischemic region.

Extension of infarction by reducing blood flow to regions containing ischemic myocardium was characterized by 1) immediate decrease or no change in the appearance of CK, depending on the time interval between initial occlusion and extension; 2) subsequent increase in CK beginning 2–5 hours after reduction in blood flow; and 3) secondary peak levels approximately 12 hours after the second occlusion. The immediate effects of reducing blood flow probably reflect effects of decreased myocardial perfusion on release of CK from infarcted myocardium; delayed increases in CK probably reflect additional myocardial necrosis. Immediate effects of decreasing blood flow to an area containing infarcted myocardium will depend on whether the infarcted myocardium is releasing CK. If release of CK from the infarcted myocardium is complete, reducing blood flow would not influence serum CK levels immediately, but would be expected to cause delayed increases in CK as a result of additional myocardial infarction. The immediate effects of reducing blood flow were also a function of the magnitude of the blood flow reduction. When proximal circumflex occlusion 6 hours after distal
occlusion resulted in only slight changes in blood flow to the lateral region of the ischemic zone (as observed in dog 4), CK levels remained virtually unchanged. The delayed increases and peak values of CK occurred at essentially the same intervals following both the distal and proximal coronary occlusion. Although the relationship was not precise in all dogs, in each dog the magnitude of the initial and delayed CK curves was proportional to the reduction in flow resulting from each occlusion.

Figure 6. Effects of extension of infarction by occlusion of the proximal circumflex coronary artery 12 hours after distal occlusion on serial serum CK activity (IU/l) in the five dogs described in figure 4. The arrows indicate the time of proximal occlusion.

Figure 7. Effect of extension of infarction by occlusion of the proximal circumflex coronary artery 6 hours after distal occlusion on serial serum CK activity (IU/l) in the four dogs described in figure 5. The arrows indicate the time of proximal occlusion.
Blood flow to the regions containing ischemic myocardium frequently increased in the interval from distal to before proximal occlusion and proximal occlusion to 24 hours after distal occlusion. Previous studies described increases in blood flow to regions containing ischemic myocardium soon after occlusion. This apparent increase in blood flow may represent increases in blood flow to ischemic myocardium via the collateral vasculature, increasing blood flow to nonischemic myocardium in the region sampled and/or differential loss of microspheres from the early microsphere injections. Increases in blood flow to nonischemic myocardium in the regions would not entirely explain the increases in blood flow, since blood flow to regions containing ischemic myocardium commonly increased when flow to anterior nonischemic samples decreased or remained unchanged. Some investigators have reported microsphere loss from infarcted myocardium while others have not observed microsphere loss. Greater microsphere loss from the earlier microsphere injections would artificially increase later blood flow measurements relative to early injections. At postmortem examination, the vessels were tightly occluded by the snare occluder, so it is unlikely that increases in flow resulted from a loose ligature in our studies.

The frequency of enzyme sampling necessary to detect infarct extension was a function of the time from the initial coronary occlusion to initiation of the intervention causing extension of infarction. The alterations in enzyme curves were characterized best by analysis of serum samples obtained at frequent intervals, i.e., optimum sampling at 1-2-hour intervals. Alterations in the enzyme curves resulting from extension of infarction were detected by analysis of serum samples obtained at 4-hour intervals, but frequently were not apparent when samples were analyzed at 8-hour intervals, especially in dogs subjected to 6- and 12-hour extension. Extension of infarction 18 hours after initial infarction could be detected by secondary increase in CK in samples obtained at 12-hour intervals.

Shell et al. have described serial changes in serum CK during certain interventions during the course of acute myocardial infarction in experimental animals and patients. Enzyme values during early increase in CK were used to predict the subsequent CK curves based on nonlinear curve-fitting techniques. Certain deviations from the anticipated or projected curves were interpreted as indicative of extension of infarction or protection of ischemic myocardium. Propranolol administered 5 hours after coronary artery occlusion (and thus during the rapid rise phase of CK) resulted in immediate decreases in CK levels that fell below the projected curves and delayed increases in CK; peak levels occurred approximately 10 hours later. The immediate reduction in CK was interpreted as salvage of myocardium and the delayed peak as extension of infarction. It was concluded that propranolol resulted in salvage of myocardium in 50% of the animals studied. In another study, reduction in blood flow with trimethaphan in hypertensive patients with acute myocardial infarction was accompanied by an initial rapid decrease in serum CK to values below those predicted from the initial CK curve. CK values then fell along a plateau for approximately 10 hours before they decreased. It was concluded that trimethaphan
reduced infarct size approximately 24% compared with the predicted size.

In experimental studies, increases in heart rate by pacing or isoproterenol infusion at specified intervals after initiation of infarction raised CK activity above the projected enzyme curves. Studies from this laboratory and others have demonstrated that increasing blood flow to a myocardial region subjected to prolonged ischemia results in immediate and rapid increases in serum CK activity. Interventions that affect myocardial perfusion seem to cause two changes in CK activity, one immediate and one delayed. Immediate changes in serum CK activity may indicate increases or decreases in blood flow to infarcted myocardium which continues to release CK. Development of delayed changes in CK will depend on whether the decreased perfusion causes further necrosis. The CK pattern for intervention that increases blood flow to an ischemic area but extends infarction, e.g., isoproterenol infusion, may be a combination of immediate and delayed changes in CK activity. Interventions that decrease blood flow without increasing ischemic injury may decrease CK immediately without producing a delayed increase in CK. Thus, immediate increases in CK activity cannot be equated with extending infarction (or deleterious effect of intervention), and decreases in CK activity cannot be equated with reduction of infarction or salvage of ischemic myocardium.

In the present study we examined the effects of infarct extension on serial CK measurements; we did not use initial increases in CK measurements to predict or project the subsequent CK curves. Nonlinear curve-fitting techniques were not used. In this study, as in other studies from this laboratory, there was not a close relationship between the CK estimates and infarct size and histologically confined necrosis. In general, our findings confirm that CK activity does not relate well to infarct size in large infarcts (more than 20 g). In this study only three dogs had small infarcts. In the 11 dogs with large infarcts, CK appearance was variable, and in many instances was relatively less than that observed in the dogs with smaller histologic infarction. Regional myocardial blood flow patterns may explain this finding. In recent studies from this laboratory, the larger infarcts were characterized by central zones of severe ischemia with low blood flow persisting for 24 hours after occlusion; reduced CK appearance in large infarcts may be accounted for by the severely impaired blood flow.

Certain reports have indicated that after permanent coronary artery occlusion there is significant loss of microspheres from the infarcting myocardium, while others have not observed significant microsphere loss. The studies that have reported microsphere loss also reported that approximately 25% of the microspheres injected before infarction were lost from the infarcted region at 24 hours. No further loss occurred at 4 or 8 days. Since we made blood flow measurements at different intervals after coronary artery occlusion, microsphere loss from earlier injections may have been greater than that from later injections. Consequently, blood flow values may have been 20–30% higher than the values recorded, and earlier blood flow measurements may have been higher than later values. The blood flow values used to establish extension of infarction were obtained 2 hours after the blood flow values measured before extension. Microsphere loss probably did not significantly alter the relationship between the blood flow measurements before and after extension.

The results from this study indicate that extension of myocardial infarcts by reducing blood flow to an ischemic region produces immediate and delayed alterations in serum CK activity. Significant reduction in blood flow resulted in immediate decrease in CK values 6 and 12 hours after occlusion, but not at 18 hours. These data suggest that immediate effects of reducing blood flow to an ischemic region are a function of whether the infarcted myocardium is in a period of CK release, i.e., 6 and 12 hours, or CK release is completed, i.e., possibly by 18 hours. Extension of infarction by significant reduction in blood flow at each interval resulted in delayed increases in CK activity beginning 2–5 hours after occlusion. Peak values occurred 12 hours after occlusion. The intervals between initial increases and peak values of CK following the secondary occlusion were essentially the same as those observed following the initial occlusion. The immediate effects of extension of infarction by reducing blood flow reflects the effect of perfusion on release of CK from infarcted myocardium, not extension of infarction. Delayed effects of reducing blood flow result from additional myocardial necrosis, and thus represent true extension of infarction. In each dog the magnitude of both the immediate and delayed CK changes was proportional to the magnitude of the ischemia produced by each occlusion. Our results suggest that interventions that directly or indirectly affect myocardial perfusion may produce similar immediate and delayed effects on serial CK measurements.

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