Regional Myocardial Blood Flow during Graded Treadmill Exercise following Circumflex Coronary Artery Occlusion in the Dog

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SUMMARY We evaluated the functional capacity of the intercoronary collateral vasculature in response to graded exercise 2 weeks after acute circumflex coronary artery occlusion. Acute myocardial infarction was produced in 11 chronically instrumented awake dogs by abrupt occlusion of the left circumflex coronary artery. Two weeks later regional myocardial blood flow was measured at rest and during three levels of graded treadmill exercise by injection of radionuclide-labeled microspheres, 7-10 μm in diameter, into the left atrium. The region of collateral-dependent myocardium was determined by injection of Evans blue dye into the coronary artery distal to the occluder, and the extent of infarction by histological examination. At rest, blood flow to collateral-dependent regions was directly proportional to the amount of viable myocardium present. In regions containing <25% infarcted myocardium, blood flow increased progressively with exercise as in normally perfused control areas from the anterior left ventricular wall. In regions containing >75% infarcted myocardium, blood flow did not increase significantly during exercise, and in over one-half flow during exercise, actually fell below the resting level. In areas containing 26-75% infarcted myocardium, blood flow demonstrated an intermediate ability to increase in response to exercise. Thus, the capacity of the coronary collateral circulation to deliver blood to its dependent myocardium was compromised progressively in proportion to the degree of infarcted myocardium. Collateral-dependent areas containing relatively small proportions of infarcted myocardium had normal blood flow response to exercise, whereas regions containing extensive infarction had little or no functional reserve so that increasing hypoperfusion commonly occurred during exercise. Circ Res 47: 59-68, 1980

Although abrupt total occlusion of a major coronary artery consistently leads to acute myocardial infarction, the resultant infarct generally is considerably smaller than the area of myocardium normally perfused by the occluded artery (Mautz and Gregg, 1937; Schaper et al., 1969). Thus, Schaper and associates (1969) found that occlusion at the midportion of the left anterior descending coronary artery in dogs resulted in myocardial infarction involving 11.2 ± 4.1% of the left ventricular mass, whereas injection techniques showed that this artery supplied 20.1 ± 5.3% of the left ventricular muscle. Survival of a portion of the myocardium normally perfused by an occluded coronary artery is dependent on delivery of a limited inflow of arterial blood by preexisting intercoronary collateral vasculature; the proportion of myocardium surviving acute coronary occlusion is related quantitatively to the volume of collateral inflow available to the acutely ischemic myocardium early after coronary occlusion (Rivas et al., 1976; Bishop et al., 1976). Although coronary occlusion is followed by gradual growth of the preexisting collateral vasculature, development of a mature intercoronary collateral system requires 3-6 months (Schaper, 1971). Thus, existence of an area of myocardium early after coronary occlusion which is viable but dependent on an immature collateral system suggests that this area may be vulnerable to further ischemic insult if (1) the myocardial oxygen requirement is increased beyond the limited capacity of the collateral vessels to deliver arterial inflow, (2) collateral inflow is decreased, possibly by diversion of arterial blood away from the collateral-dependent myocardium to normally perfused areas during periods of stress, or (3) by a combination of both effects.

The present study was undertaken to evaluate the relationship between blood flow and the degree of infarction in collateral-dependent areas of myocardium. The ability of blood flow to increase during exercise was examined for evidence of stress-induced perfusion deficits in collateral-dependent areas of myocardium. Studies were carried out in chronically instrumented awake dogs 2 weeks after acute myocardial infarction had been produced by abrupt occlusion of the left circumflex coronary artery. This interval was chosen since it corresponds to a time at which patients hospitalized for...
Acute myocardial infarction often are discharged from the hospital to increase their level of exercise.

**Methods**

Eighteen adult mongrel dogs weighing 18–27 kg were anesthetized with sodium thiopental (25 mg/kg, iv) and ventilated with a Harvard respirator (Harvard Apparatus Company, Inc.). A left thoracotomy was performed in the 4th intercostal space, and a polyvinyl chloride catheter, 3.0 mm o.d., was inserted in the left atrial cavity via the arterial appendage and secured with a purse string suture. A polyvinyl chloride catheter, 3.5 mm o.d., was inserted into the root of the aorta via the left internal thoracic artery. Both catheters were filled with heparin at a concentration of 1000 U/ml. The left circumflex coronary artery was dissected free just distal to the 1st left ventricular branch, and a snare type occluder was positioned around the artery (Rivas et al., 1976). The catheters and occluders were tunneled to a subcutaneous pouch at the base of the neck. Following recovery from surgery, the dogs were trained to run on a motor driven treadmill (model 1849-D, Quinton Instrument Company).

Seven to 26 days after the initial surgery (mean = 18 ± 2.3 days), the dogs were returned to the laboratory for production of acute myocardial infarction. The snare was exteriorized from the subcutaneous pouch with 2% lidocaine infiltration anesthesia. Lead II of a standard electrocardiogram was monitored continuously. Morphine sulfate (5 mg, iv) was administered immediately prior to coronary occlusion and repeated 10–15 minutes later to minimize discomfort resulting from the coronary occlusion. A bolus injection of lidocaine (2 mg/kg, iv) was administered to minimize early arrhythmias; additional dosages of lidocaine (1 mg/kg, iv) were repeated at 15-minute intervals for the first hour. Arrhythmias occurring after the first hour of occlusion were not treated. The coronary occluder was then tightened to produce total coronary artery occlusion. In every case this resulted in prompt appearance of marked S-T segment elevation on the electrocardiogram. Two dogs developed intractable ventricular fibrillation within 15 minutes after coronary artery occlusion and were excluded from the study. Three dogs died, one each 14, 24, and 26 hours after the occlusion, and were found to have total occlusion of the circumflex coronary artery and histological evidence of early myocardial infarction of the posterior left ventricular wall. Two more dogs died 13 and 14 days after occlusion and were found to have total occlusion of the circumflex coronary artery with transmural myocardial infarction involving the posterior left ventricular wall. Studies of regional myocardial blood flow were performed at rest and during exercise in the 11 surviving dogs. After coronary occlusion, the dogs were exercised for approximately 10 minutes twice weekly to maintain their familiarity with the treadmill.

Measurements of regional myocardial blood flow were performed 13–17 days after coronary occlusion (mean = 14.5 ± 0.4 days after occlusion). On the morning of study, the left atrial and aortic catheters were exteriorized from the subcutaneous pouch with 2% lidocaine infiltration anesthesia. The arterial catheter was attached to a Statham P37Db pressure transducer mounted on the dog's side; in addition, a polyethylene tube connected the arterial catheter to a Harvard Apparatus model 1210 constant rate withdrawal pump to facilitate obtaining the reference arterial blood samples. The left atrial catheter was connected by a stiff polyethylene tube to a Statham P23Db pressure transducer mounted on a treadmill cage at mid-chest level. Phasic and mean arterial pressures and mean left atrial pressure were recorded continuously on a Hewlett-Packard model 7700 direct-writing oscillograph.

Measurements of regional myocardial blood flow were made by means of serial injections of microspheres 7–10 μm in diameter labeled with γ-emitting radionuclides 141Ce, 51Cr, 85Sr, and 46Sc. The microspheres were diluted in 10% low molecular weight dextran so that 1.5 ml (the volume injected) contained approximately 3 × 10⁶ microspheres. Before injection, the microspheres were mixed for at least 15 minutes in an ultrasonic bath and a vortex agitator. During each intervention, 1.5 ml of the microsphere suspension were injected into the left atrium over a 15-second interval, and the atrial catheter was flushed with 10 ml of isotonic saline. Beginning 5 seconds before each microsphere injection and continuing for 90 seconds, a reference sample of arterial blood was withdrawn from the aortic catheter at a constant rate of 15.0 ml/min. Injections of microspheres resulted in no change in heart rate during the interval of injection and no change in aortic or left atrial pressure measured immediately before and after collection of the reference blood sample.

Measurements of myocardial blood flow were made during quiet resting conditions while the dog was standing, and during light, moderate, and heavy exercise on the treadmill. Light exercise was defined as the speed and grade necessary to increase heart rates to 140–170 beats/min. Moderate exercise was regulated to increase heart rates to 180–220 beats/min. Heavy exercise was the level of exercise necessary to achieve heart rates greater than 220 beats/min. The mean speed and grade for each exercise were: light exercise 2.1 mph and 1% grade; moderate exercise 4.0 mph and 2.3% grade; and heavy exercise 5.5 mph and 6% grade. Microspheres were injected 2 minutes after a steady level of heart rate and arterial blood pressure had been achieved during each exercise intervention. This interval was chosen since previous studies have demonstrated that coronary artery blood flow may be expected to reach...
a steady state within 10–20 seconds after the onset of exercise (Khoury et al., 1965; VanCitters and Franklin, 1969; Ball et al., 1975). Exercise was continued for 2 minutes after completion of the microsphere injection to ensure that steady state conditions existed while microspheres were cleared from the circulation. A minimum interval of 20 minutes was allowed between exercise interventions.

After the study had been completed, the dog was anesthetized with sodium thiopental (30 mg/kg, iv) and ventilated with a respirator, and a left thoracotomy was performed via the intercostal space below the previous incision. The region of the coronary artery just distal to the occluder was dissected free and cannulated with 20- and 26-gauge needles. The 26-gauge needle was attached to a pressure transducer and 15 ml of Evans blue dye were injected through the 20-gauge needle at pressures equal to aortic pressure.

The heart was then removed, weighed, and fixed in 10% buffered formalin. The lumina of the proximal circumflex coronary artery was examined to verify total occlusion by the snare. The great vessels, atria, right ventricle, large epicardial blood vessels, and epicardial fat were dissected from the left ventricle. Mean heart weight was 165 ± 2.7 g, whereas mean left ventricular weight was 95.8 ± 3.0 g. The left ventricle was then sectioned into four transverse rings of equal thickness from base to apex as previously described (Rivas et al., 1976). The two central rings were divided into six circumferential regions corresponding to the anterior left ventricular wall, interventricular septum, posterior wall, posterior papillary muscle region, lateral wall, and anterior papillary muscle region. The blue-stained area corresponded to the posterior wall, anterior, septum, posterior, and lateral regions. Each specimen then was divided into four transmural layers of equal thickness from epicardium to endocardium. This was done to ensure that the posterior papillary muscle specimens did not include peninsulas of normally perfused myocardium and were, therefore, completely collateral dependent. The basal and apical left ventricular rings were each divided into four specimens representing anterior, septum, posterior, and lateral regions. Each specimen was then divided into four transmural layers of equal thickness from epicardium to endocardium; the resultant specimens weighed 1–2 g. For the remainder of this paper, these layers will be referred to as “layers 1 to 4,” layer 1 being the most epicardial layer and layer 4 the most endocardial layer. Each specimen was placed in a counting vial and 10% buffered formalin was added to preserve the tissue for later histological study. Myocardial and blood reference samples were counted in a γ spectrometer at window settings selected to correspond to the peak energies of each radionuclide. The activity recorded in each energy window was corrected for background activity and overlapping counts contributed by the accompanying isotopes. Blood flow (ml/min) to each sample was computed with the formula: \( F_m = F_r \cdot C_m/C_r \), where \( F_m \) = sample blood flow (ml/min), \( F_r \) = reference blood flow (ml/min), \( C_m \) = counts/min of the myocardial sample, and \( C_r \) = counts/min of the reference flow sample. Each sample blood flow (ml/min) was divided by the sample weight and expressed as ml/min per g of myocardium.

After blood flow measurements had been obtained, the myocardial specimens were prepared for histological examination by recombining the four tissue samples from each circumferential region into the original transmural sequence. The recombined myocardial specimens were embedded in paraffin, and histological sections 8 μm thick were obtained and stained with hematoxylin and eosin. A minimum of two sections were taken at different depths in each tissue block for determination of the average extent of infarction. The percentage of infarcted myocardium in each tissue sample was determined using grid markers. Infarcted myocardium was characterized by partial or complete cellular dissolution, inflammatory cell infiltrate, and loss of normal cellular architecture. Since the infarcts in this study were approximately 2 weeks of age, infarcted myocardium was delineated clearly from normal tissue and analyzed easily by the use of routine hematoxylin and eosin stains. Each histological section was analyzed by two observers, and the extent of infarction was taken as the average of these two determinations. If the extent of infarction determined by the two observers differed by more than 10%, the section was reviewed and the percentage of infarct recomputed. This degree of observer variability occurred in approximately 5% of the specimens.

Heart rate, aortic pressure, and left atrial pressure were measured directly from the strip chart recordings. Comparisons between values obtained at rest and during the three levels of exercise were performed using Student’s \( t \)-test for paired data; the resultant \( P \) values were adjusted using the Bonferroni inequality which corrects for performing multiple tests on correlated data (Miller, 1966). Blood flow data for individual myocardial specimens were examined by an analysis of variance performed on each of the collateral-dependent regions (posterior wall, posterior papillary muscle, and lateral wall). Since tests of the hypothesis of equal stress means (rest and the three levels of exercise) and of equal layer means both were significant at a probability level of less than 0.05, multiple comparisons of the various sets of means were carried out according to the method of Tukey, which adjusts for performing multiple comparisons on correlated data (Brownlee, 1960). To examine...
the effect of percentage infarction within a tissue specimen on the response of myocardial blood flow during exercise, we grouped tissue sections containing 1%–25%, 26%–50%, 51%–75%, and 76%–100% infarcted myocardium each as a block, and blood flow at rest and during the three levels of exercise was compared by the method of Tukey which adjusts for performing multiple comparisons (Brownlee, 1960).

**Results**

Table 1 lists mean hemodynamic data from 11 dogs during quiet resting conditions and at three levels of treadmill exercise. During resting conditions, heart rates ranged from 60 to 126 beats/min, mean arterial pressures were 88 to 120 mm Hg, and left atrial pressures were 0 to 10 mm Hg. During light exercise (heart rates 141 to 185 beats/min), mean arterial pressure ranged from 88 to 120 mm Hg and was significantly increased above the resting level (P < 0.01). During moderate exercise (heart rates 189 to 222 beats/min), mean arterial pressure ranged from 87 to 140 mm Hg and was significantly increased above the resting level (P < 0.01). Mean left atrial pressure increased significantly from rest to light exercise (P < 0.03) and underwent an additional significant increase from light to heavy exercise (P < 0.05).

Chronic occlusion of the circumflex coronary artery distal to the first left ventricular branch resulted in a variable degree of myocardial infarction involving 0.2 to 22.1% of the left ventricle (mean infarct size = 7.6 ± 2.2 g). As shown in Table 2, infarction was confined to the posterior free wall, posterior papillary muscle region, and lateral wall specimens, with the greatest degree of infarction occurring in the posterior papillary muscle region. In all involved regions, there were significant progressive increments in the degree of infarction from layer 1 to layer 2, from layer 2 to layer 3, and from layer 3 to layer 4 (each P < 0.01).

During resting control conditions, mean myocardial blood flow to the anterior free wall, anterior papillary muscle region, and interventricular septum specimens (those areas not supplied by the circumflex coronary artery) was 1.07 ± 0.07 ml/min per g (Table 2). Although the average blood flow to layer 4 (endo) exceeded flow to layer 1 (epi), resulting in a mean endo:epi ratio of 1.10, this value was not significantly different from unity. As shown in Figure 1, blood flow to the anterior wall, anterior papillary muscle region, and interventricular septum increased regularly with increasing exercise, and these increases were similar in all four transmural layers, resulting in no significant change in the endo:epi ratios. The increase in myocardial blood flow (MBF) was linearly related to heart rate (HR) in these uninvolved myocardial regions (MBF = 0.0157 HR – 0.506; r = –0.74).

**Table 1 Hemodynamic Data**

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Aortic pressure (mm Hg)</th>
<th>Left atrial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93 ± 6</td>
<td>82 ± 3</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td><strong>Light exercise</strong></td>
<td>164 ± 4*</td>
<td>101 ± 3*</td>
</tr>
<tr>
<td>206 ± 6†</td>
<td>118 ± 5†</td>
<td>8.4 ± 2.4†</td>
</tr>
<tr>
<td><strong>Heavy exercise</strong></td>
<td>242 ± 6‡</td>
<td>129 ± 6‡</td>
</tr>
<tr>
<td>9.1 ± 2.6†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* P < 0.05 in comparison with the corresponding value obtained at rest.
† P < 0.05 in comparison with the corresponding value obtained during light exercise.
‡ P < 0.05 in comparison with the corresponding value obtained during moderate exercise.

**Table 2 Myocardial Blood Flow to Six Left Ventricular Regions during Quiet Resting Conditions.**

<table>
<thead>
<tr>
<th>Layer</th>
<th>AP anterior wall</th>
<th>Inter-ventricular septum</th>
<th>Posterior free wall</th>
<th>PP muscle region</th>
<th>Lateral wall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood flow (ml/min per g)</td>
<td>Blood flow (ml/min per g)</td>
<td>Blood flow (ml/min per g)</td>
<td>Blood flow (ml/min per g)</td>
<td>Blood flow (ml/min per g)</td>
</tr>
<tr>
<td>AP muscle region</td>
<td>1.00±0.10</td>
<td>0.97±0.11</td>
<td>0.94±0.08</td>
<td>2.2±1.1</td>
<td>0.91±0.13</td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>1.08±0.08</td>
<td>1.12±0.03</td>
<td>1.12±0.09</td>
<td>9.7±3.4</td>
<td>0.86±0.14†</td>
</tr>
<tr>
<td>Posterior free wall</td>
<td>1.14±0.11</td>
<td>1.09±0.11</td>
<td>1.17±0.08</td>
<td>26.2±3.3</td>
<td>0.82±0.14†</td>
</tr>
<tr>
<td>PP muscle region</td>
<td>1.08±0.10</td>
<td>1.06±0.11</td>
<td>1.08±0.08</td>
<td>35.1±8.0</td>
<td>0.77±0.14†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. AP = anterior papillary; PP = posterior papillary.
* In addition, the percent myocardium infarcted in the three regions supplied by the occluded circumflex coronary artery is indicated. Within each region the myocardium was divided into four layers from epicardium (layer 1) to endocardium (layer 4).
† Denotes P < 0.05 in comparison with blood flow to the corresponding normally perfused myocardial region.
‡ Denotes P < 0.01 in comparison with blood flow to the corresponding normally perfused myocardial region.
During resting control conditions, blood flows to all layers of the posterior papillary muscle region, layers 2, 3, and 4 of the posterior free wall, and layers 3 and 4 of the lateral left ventricular wall specimens were decreased significantly below the flows to the corresponding normally perfused myocardial regions \( (P < 0.01) \) (Table 2). The reduction of blood flow to the involved myocardial areas increased progressively from epicardium to endocardium resulting in endo:epi ratios of 0.84, 0.52, and 0.84 in the posterior wall, posterior papillary muscle region, and lateral wall, respectively. All of these ratios were significantly less than 1.0 and significantly less than for the corresponding normally perfused areas \( (P < 0.01) \). As shown in Table 2, blood flow to the involved areas of myocardium varied in relation to the amount of remaining viable myocardium. In Figure 2, blood flow during resting conditions is plotted against the percent infarct for each specimen containing infarcted myocardium in all 11 dogs; a total of 237 specimens contained infarcted myocardium. A significant inverse relationship existed between the percent of myocardium infarcted and absolute myocardial blood flow \( (r = -0.74) \). There was no difference in the degree of reduction of blood flow for a given percentage of infarction across the four transmural layers, so that the relationship between blood flow and extent of myocardial infarction was not influenced by the transmural position of the myocardial specimen.

Blood flow to the posterior and lateral wall specimens increased regularly with each increase in exercise level, although the increase in blood flow in layers 3 and 4 did not achieve statistical significance between moderate and heavy exercise (Fig. 1). In the posterior papillary muscle region, a significant progressive redistribution of flow occurred during exercise with the endo:epi ratio falling from 0.52 at rest to 0.27 during heavy exercise. Although blood flow to layer 1 of the posterior papillary muscle region increased significantly with each increment in exercise, and flow to layers 2 and 3 increased from rest to moderate exercise \( (each \ P < 0.05) \), no significant increase occurred either from rest to light exercise or from moderate to heavy exercise in layers 2 or 3. Blood flow to layer 4 did not increase significantly during light or moderate exercise, and actually showed a decrease from moderate to heavy exercise in eight of the 11 dogs studied, although this decrease did not achieve sta-
Statistical significance. As shown in Figure 3, the response of blood flow to exercise was related to the degree of infarcted myocardium. Areas containing 25% or less infarcted myocardium showed regular increases in blood flow with each increment in exercise, whereas areas containing more than 75% infarcted myocardium showed no significant ability to increase blood flow during exercise. The areas containing intermediate degrees of infarction showed a corresponding intermediate ability to increase blood flow with exercise.

When the change in blood flow during exercise was related to the degree of infarcted tissue within individual myocardial specimens, it was found that specimens that showed regular progressive increases in blood flow with each level of exercise contained relatively small amounts of infarcted tissue (mean infarction = 19 ± 4.1%; range = 1 to 49% infarction). In contrast to this, 31 of the 237 specimens containing infarcted myocardium demonstrated a small increase in blood flow with light or moderate exercise, but flow rates during heavy exercise were decreased below the resting control level. These specimens contained an average of 91 ± 4.8% infarcted myocardium (range = 72 to 100% infarcted myocardium). Thirty-three specimens showed a significant increase in blood flow during light exercise with a lesser increase during heavier levels of exercise although, at all levels of exercise, flow increased above the resting level. The degree of infarcted myocardium in these specimens was intermediate (average infarction = 78 ± 5.2%, range = 59-93%). Since the degree of infarction was greatest in the deeper myocardial layers, the tendency for flow to decrease during exercise was observed most commonly in the layers nearest the endocardium. Figure 4 demonstrates this by illustrating blood flow to the four transmural layers of the posterior papillary muscle region of a dog with progressively increasing degrees of infarction from layers 1 through 4. Blood flow to layers 1 and 2, which showed 9 and 27% infarction, respectively, increased progressively with each increment in exercise. In contrast to this, blood flow to layer 3 (which contained 69% infarcted myocardium) showed an initial increase in blood flow with light and moderate degrees of exercise, with a lesser ability to augment blood flow during heavy exercise. Layer 4, which contained 75% infarcted myocardium, showed a slight increase in blood flow during light exercise, but during moderate and heavy exercise blood flow decreased below the light exercise value.

Discussion

Numerous previous studies have demonstrated that an intercoronary collateral circulation is functional immediately after sudden coronary artery occlusion in the dog (Gregg et al., 1939; Kattus and...
Gregg, 1959; Levy et al., 1961). Measurements of myocardial blood flow during the first 2 hours after acute coronary occlusion have shown that the amount and distribution of collateral flow determines the extent and location of myocardium which is protected from irreversible cell damage (Rivas et al., 1976; Bishop et al., 1976). In contrast to the almost invariable occurrence of myocardial infarction following sudden total occlusion of a major coronary artery, if the occlusion is applied gradually (either by means of an externally controlled occluder cuff or with an Ameroid arterial constrictor), the preexisting collateral channels are able to undergo sufficient growth to protect the collateral-dependent myocardium from infarction despite ultimate development of total coronary artery occlusion (Elliot et al., 1968, 1970; Becker and Pitt, 1971). Although the collateral channels are able to provide sufficient arterial inflow to prevent infarction during gradual coronary occlusion, initially there is little or no reserve capacity for increasing flow to the collateral-dependent myocardium in response to vasodilator stimuli (Schaper et al., 1973). In studies of the histology of the collateral vasculature, Schaper (1971) demonstrated that, early after Ameroid occlusion of the circumflex coronary artery in dogs, the intercoronary collateral vessels become thinned and dilated, taking on the appearance of overstretched arterioles. Subsequent mitotic activity within the vessel wall results in transformation of these collateral channels into well-developed arteries within 6–12 months after occlusion. This continuing vascular growth results in increasing capacity for blood flow so that at 6–12 months after total coronary occlusion, the collateral vessels are able to provide normal increases in blood flow to collateral-dependent myocardium in response to moderate levels of treadmill exercise in dog (Lambert et al., 1977).

Most previous studies of collateral function in hearts with chronic coronary occlusion have employed Ameroid arterial constrictors which avoid the considerable mortality rate associated with abrupt total coronary artery occlusion (Schaper, 1971; Becker and Pitt, 1971; Schaper et al., 1973; Lambert et al., 1977). Water absorption causes swelling of the hygroscopic Ameroid material to compress progressively the arterial lumen with total occlusion generally occurring within 3–6 weeks (Schaper, 1971). In the dog, this technique results in a collateralized area of myocardium, generally without production of myocardial infarction. However, since ischemic injury to the intramyocardial vasculature appears to be an important component of the infarction process and reasonably may be expected to influence the subsequent ability of blood flow to increase, the present study was undertaken to observe blood flow in collateral-dependent myocardium which included areas of infarction (Cobb et al., 1976; Hirzel et al., 1976). In addition to examining the relationship between blood flow and the degree of viable myocardium after resolution of the acute infarction process, the ability of blood flow in the collateral-dependent area to increase in response to exercise stress was studied. We chose to perform these studies 14 days after acute coronary occlusion, since, in the clinical situation, discharge from the hospital and increased activity are common at this interval after acute myocardial infarction. Thus, the functional reserve capacity of the collateral vasculature to increase blood flow in response to the physiological stress of exercise was examined early in the course of collateral vessel development.

Several technical aspects of the present study which may have resulted in experimental error must be considered. First, use of the microsphere technique requires that an adequate number of particles be delivered to the specimens under consideration to minimize error associated with random distribution variability. Buckberg et al. (1971) demonstrated that random measurement error increases markedly as the number of microspheres within a given specimen fell below 400. In our study, myocardial regions containing high percentages of infarcted tissue had low flow rates at which such random variability potentially could be troublesome. However, previous studies, in which simultaneous injection of several different species of microspheres was used, have shown that, although the reduced delivery of microspheres to hypoperfused areas increased measurement variability expressed as percentage differences, such variability resulted in only small differences in absolute blood flow measurements (Rivas et al., 1976). For example, in areas with measured flows below 0.10 ml/min per g of myocardium, the average measurement error was only 0.01 ± 0.003 ml/min per g (Rivas et al., 1976). Thus, even relatively small changes in absolute flow rates to hypoperfused areas would be detectable with serial microsphere injections. A second potential error relates to determination of the percentage of infarcted myocardium within each tissue specimen. Since the myocardial tissue was not examined until 2 weeks after acute coronary occlusion, infarcted myocardium was readily discernable from normal myocardium, by means of routine histological staining techniques. As previously reported, the boundary between viable and infarcted myocardium was found to be irregular and characterized by intermingling of intact with infarcted myocardium (Rivas et al., 1976; Cobb et al., 1976). Because of this spatial variability of the infarct boundary, the percentage infarct was estimated from a minimum of two histological sections from each side of each tissue block. If differences greater than 10% were found between sections, additional sections were cut and analyzed. In addition, the percentage infarct was estimated by two independent microscopists; when a difference of more
than 10% was recorded by the two observers, the sections were reexamined. A difference of more than 10% occurred in only 10 of the 237 tissue specimens that contained infarct.

A third potential problem relates to the completeness of trapping of microspheres in areas containing infarcted myocardium. Although it is clear that trapping of microspheres in the normal heart is virtually complete (Cobb et al., 1974), recent studies have demonstrated that microspheres injected at the time of acute coronary artery occlusion appear to be partially lost during the ensuing 24 to 48 hours (Jugdutt and Becker, 1977; Capurro et al., 1979). This loss of microspheres may be a function of the inflammatory process associated with acute myocardial infarction, since loss of microsphere activity did not occur during the first hour after injection, but was apparent 24 to 48 hours later. Although direct measurement of the degree of microsphere shunting in normal vs. infarcted tissue could not be performed in the present study, the measurements were made at a time when the acute inflammatory process had subsided. In addition, successive doses of microspheres were delivered in close temporal proximity, the interval from injection of the first microspheres to the last injection being less than 2 hours, and the animals were killed immediately thereafter.

Results from the present study indicate that during control conditions blood flow into the collateral-dependent area of myocardium was related directly to the amount of residual viable myocardium within a left ventricular specimen. The relationship between blood flow and the amount of viable myocardium present in a given area was unaffected by the transmural location of the myocardial specimen. This is in contrast to our previous finding that, when microspheres were injected within the first 24 hours after acute coronary artery occlusion, for a given reduction in measured blood flow, the extent of infarct was greater in the subendocardium than in the subepicardium. Failure to observe a similar influence of transmural position on the relationship between the degree of infarction and blood flow in the present study suggests that this relationship may change as the infarct matures. In addition, in the earlier study, the microspheres were injected during the acute infarction process, so that loss of microsphere activity could have distorted the blood flow measurements (Jugdutt and Becker, 1977; Capurro et al., 1979).

More interesting than the direct relationship between collateral perfusion and the degree of viable myocardium observed during resting conditions was the response of blood flow to graded exercise. In normally perfused areas of myocardium, blood flow increased regularly during exercise as a direct function of heart rate in a manner similar to that previously reported in normal dogs (Ball et al., 1975). In collateral-dependent regions, myocardial blood flow increased with light exercise and, in the majority of areas, flow continued to increase with heavier exercise loads. However, in some areas containing extensive infarction, blood flow did not continue to increase with increasing exercise, and, in certain specimens, flow during heavy exercise fell to levels below those observed during resting conditions. It is probable that failure of blood flow to continue to increase during progressive increases in exercise level represents a perfusion abnormality. Moreover, the finding that blood flow actually decreased with increasing exercise in some involved areas, when the metabolic requirements of the residual viable muscle would be expected to continue to increase (and surely not decrease), suggests exercise-induced hypoperfusion. These data indicate that, although collateral blood flow was capable of increasing in response to increased myocardial needs, this reserve capacity is limited in areas with moderate degrees of infarction and may be grossly inadequate in areas with extensive infarction.

Why would hypoperfusion occur in certain collateral-perfused areas, whereas blood flow to other parallel collateral-dependent regions continued to increase in response to increasing levels of exercise? Since net inflow to the collateral-dependent region of the left ventricle continued to increase in response to increasing levels of exercise, it would appear that the problem is one of distribution of the available blood flow. Within the limits of the collateral channels to deliver blood, regulation of the volume and distribution of blood flow will be controlled by the resistance vessels of the collateral-dependent myocardium. However, as the resistance vessels vasodilate in an attempt to increase arterial inflow in response to the increasing myocardial oxygen requirements during exercise, maximal local vasodilation may be achieved, and the collateral channels then will become flow-limiting. In this situation, when the resistance vessels have become maximally vasodilated, local vasomotion no longer will be able to participate in regulation of the distribution of blood flow in the collateral-dependent areas. Loss of vasomotor activity within the collateral-dependent area will result in blood flow distribution being determined by the physical factors which influence perfusion across the left ventricular wall in systole and in diastole (Bache and Cobb, 1977). Since the areas of the left ventricle containing extensive infarction in which perfusion abnormalities became apparent during moderate or heavy exercise were invariably located in the deeper myocardial layers, these regions would be subject to the factors that influence subendocardial perfusion. The most readily apparent change in the factors influencing transmural myocardial perfusion that occurred during exercise was an increase in heart rate which caused a decrease in the interval of diastole when subendocardial perfusion can occur (Buckberg et al., 1972; Russell et al., 1977). Thus, the interval of diastole was 41.0 sec/min during resting conditions with a heart rate of 92 beats/min.
and decreased to a minimum of 31.6 sec/min during heavy exercise at a heart rate of 242 beats/min (a decrease of 27%). In normally perfused myocardial areas with intact vasomotor tone, the effect of this decreased interval of diastole associated with tachycardia could be countered by a selective decrease in diastolic subendocardial vascular resistance to maintain uniform net transmural perfusion (Bache and Cobb, 1977). However, no such vasomotor adjustments could occur in areas in which maximal vasodilation of the resistance vessels had occurred already in an attempt to increase collateral inflow. In addition, the significant increase in left ventricular diastolic pressures during exercise would tend to impede blood flow into the deeper myocardial layers, especially if perfusion pressure in the collateral-dependent vascular system fell to relatively low levels as coronary arteriolar vasodilation within the collateral-dependent area resulted in an increasing pressure drop across the collateral channels. In diastole, as in systole, a transmural gradient of intramyocardial tissue pressure exists across the left ventricular wall, increasing from the level of intrathoracic pressure at the epicardial surface to the level of intramyocardial tissue pressure at the endocardium (Armour and Randall, 1971; Domenech, 1978). Although this modest gradient of tissue pressure would be expected to have little effect on transmural perfusion at normal coronary artery pressure, at low coronary perfusion pressures in the collateral dependent area this gradient of diastolic myocardial tissue pressure would tend to inhibit perfusion of the deeper layers of ventricular myocardium selectively (Bache et al., 1977).

In summary, the present data suggest that when arterial inflow was unable to meet the requirement of the collateral-dependent myocardium during exercise, several factors resulted in transmural redistribution of perfusion with selective underperfusion of the deeper myocardial layers, which contained extensive areas of infarction. First, the tachycardia during exercise reduced the interval of diastole available for perfusion of the subendocardium. Second, since the vascular resistance gradient which normally favors perfusion of the subendocardium in diastole to compensate for systolic underperfusion is dependent in part upon active coronary vasomotion, intense vasodilation within the collateral-dependent area during exercise would be expected to compromise preferential perfusion of the subendocardium during diastole (Bache et al., 1977). Third, vasodilation within the collateral-dependent area during exercise would result in an increased pressure drop across the collateral channels, thereby reducing perfusion pressure within the collateralized vascular system. At very low perfusion pressures, the modest gradient of diastolic intramyocardial tissue pressure increasing from the level of intrathoracic pressure at the epicardial surface to left ventricular cavitory pressure at the endocardium would impede selectively blood flow to the subendocardium (Domenech, 1978). This transmural gradient of diastolic tissue pressure would be enhanced by the abnormal increases in left ventricular diastolic pressure which occurred during exercise in these dogs.

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References


Flow through Collapsible Tubes at Low Reynolds Numbers

Applicability of the Waterfall Model

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SUMMARY The applicability of the waterfall model was tested using the Starling resistor and different viscosities of fluids to vary the Reynolds number. The waterfall model proved adequate to describe flow in the Starling resistor model only at very low Reynolds numbers (Reynolds number < 1). Blood flow characterized by such low Reynolds numbers occurs only in the microvasculature. Thus, it is inappropriate to apply the waterfall model indiscriminately to flow through large collapsible veins. Circ Res 47: 68-73, 1980

VASCULAR collapse occurs in both small and large vessels of the circulation. Examples of blood vessels that are normally subjected to collapse are: blood vessels of the myocardium (Downey and Kirk, 1975), the skeletal muscle (Gray et al., 1967), the lung (Maloney et al., 1968), intra-abdominal veins (Guyton and Adkins, 1954), and the cutaneous veins. Pathophysiological collapse of blood vessels also can happen. For example, cerebral capillaries have been shown to collapse when intracranial pressure is increased suddenly (Hekmatpanah, 1970), and the abdominal vena cava is known to collapse when abdominal pressure is increased by ascites (Vix and Payne, 1972). Occasionally, external interventions are used to induce vascular collapse. For instance, pneumatic pressure cuffs are used to collapse the arteries of the extremities to prevent hemorrhage during surgical procedures and to measure blood pressure by producing the Korotkoff sounds heard with the stethoscope (Brooks and Luckhardt, 1916). Blood flow in the collapsible vessels of the microcirculation of the lung was first modeled in 1962 by Permutt et al. (1962) who offered a simple “waterfall model” to describe the phenomenon. They proposed that blood flow through a vessel when it is partially collapsed by tissue pressure is independent of outflow pressure, just as flow over a waterfall is independent of the height of the falls. However, Permutt et al. (1962) did not set forth the limitations of the waterfall model, thus implying that the waterfall model may be applied to any collapsible vessel. Consequently, this model has been widely quoted to explain the pressure-flow relationships of both small and large collapsible blood vessels (Downey and Kirk, 1975; Green, 1975; Mitzen, 1974; Nakhjavan, 1966).

On the other hand, the pressure-flow relationships of large blood vessels have been modeled experimentally by a “Starling resistor” physical model. This physical model takes its name from the fact that the noted physiologist, E.H. Starling...
Regional myocardial blood flow during graded treadmill exercise following circumflex coronary artery occlusion in the dog.

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