Transmural Myocardial Blood Flow in a Canine Model of Coronary Artery Bridging

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SUMMARY The purpose of the present study was to develop a canine model of coronary artery bridging and assess transmural myocardial perfusion in this setting. Six adult mongrel dogs were chronically instrumented with aortic and left atrial pressure catheters, a right ventricular bipolar pacing electrode, and a left circumflex coronary artery electromagnetic flow probe and balloon occluder. Seven to 10 days postoperatively, the animals were studied in the awake state. Myocardial bridging was modeled by totally occluding left circumflex coronary artery inflow for systole (S) only, systole plus one-sixth, one-third, and one-half of diastole (D) by means of an ECG-triggered solenoid valve, at a paced heart rate of 120 beats/min. Regional myocardial flow was determined during each intervention with 8- to 10-μm radiolabeled microspheres. No change in systemic hemodynamics was noted during the course of any occlusion intervention. However, mean left circumflex coronary flow was significantly reduced during occlusion of S + 1/3 D and S + 1/2 D, and this was associated with decreased flow to the endocardial layers. Peripheral left circumflex coronary artery pressure was assessed in an additional series of five open-chest dogs identically instrumented with the addition of a coronary artery pressure catheter inserted distal to the balloon occluder. During the occlusion of S + 1/2 D, the peripheral coronary pressure markedly decreased to a minimum value of 26 ± 5 mm Hg and a mean value of 53 ± 10 mm Hg. Thus, during the inflow time allowed by this intervention, coronary perfusion pressure was reduced markedly. If this animal model of myocardial bridging is appropriate, these data suggest that, in the rare patient with symptomatic myocardial bridging, occlusion of a coronary artery during systole and a significant portion of diastole results in a decrease in mean flow and a maldistribution of transmural flow. This blood flow deficit is related both to reduced inflow time and decreased perfusion pressure. Circ Res 49: 726-732, 1981

THE major coronary arteries and their proximal branches usually lie on the surface of the heart beneath the epicardium. Occasionally, however, a coronary vessel may penetrate the surface and follow an intramyocardial course. The vessel subsequently returns to its epicardial location distal to the point of entry. This arterial segment has, in effect, become "bridged" by the overlying myocardial tissue.

Myocardial bridging was first described by Crainicianu (1922). In 1951, Geiringer reported a 23% incidence of this anomaly in a series of 100 consecutive autopsies (Geiringer, 1951). With the advent of coronary angiography, Amplatz and Anderson (1968) observed a systolic narrowing of bridged segments, followed by a return to normal dimensions during diastole. The significance of bridging with respect to producing myocardial ischemia remained uncertain, however. Noble et al. (1976) reported clinical and metabolic evidence of ischemia in patients with myocardial bridging but otherwise normal coronary arteries. The following year, Gronin et al. (1977) described three patients with symptomatic bridging treated surgically. Of the two patients evaluated preoperatively, each demonstrated resolution of ischemic parameters postoperatively. Most recently, additional reports have appeared relating myocardial ischemia to coronary artery bridging (Faruqui et al., 1978; Raizner et al., 1980; Morales et al., 1980). Surgical correction by either supra-arterial myotomy or coronary artery bypass grafting or both has resulted in symptomatic relief and improvement of ischemic indices (Faruqui et al., 1978; Raizner et al., 1980).

The purpose of the present study was to develop a canine model of myocardial bridging in which the duration of vessel occlusion could be varied systematically over a wide range. This model was developed to simulate delayed re-opening of a bridged coronary artery segment. Systemic and coronary artery hemodynamic data were monitored and the transmural distribution of myocardial blood flow was measured by the radioactive microsphere technique.

Methods

Eleven adult mongrel dogs of either sex weighing 16-30 kg were used to develop a canine model of myocardial bridging. Six dogs (group 1) were studied in the awake state 7-10 days following instrumentation surgery. Five dogs (group 2) were studied

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as open-chest acute preparations. Detailed procedures for each group are presented below.

**Group 1**

Six dogs were anesthetized with an intravenous bolus of sodium thiamylal (30-40 mg/kg) and underwent left thoracotomy using sterile technique. Polyvinyl chloride heparin-filled catheters, 3 mm in diameter, were introduced into the ascending aorta through the left internal mammary artery and into the left atrial cavity via the appendage. The proximal 1.5 cm of the circumflex branch of the left coronary artery was dissected free, and an electromagnetic flow probe (Howell Instruments, Inc.) was positioned around the vessel. An inflatable balloon occluder, constructed in our laboratory, was placed around the circumflex vessel distal to the flow probe. An epicardial bipolar pacing electrode was sutured to the right ventricle. The catheters, occluder tubing, flow probe, and pacing leads were tunneled through the chest wall and placed in a subcutaneous pouch at the base of the neck. The thoracotomy incision was closed, and the dogs allowed to recover.

Studies were carried out 7-10 days postoperatively when the animals were active, fully recovered from surgery, and free from fever and anemia. On the morning of the study, each dog received an intramuscular injection of 10 mg morphine sulfate and a subcutaneous injection of 1% lidocaine hydrochloride and the epicardial blood vessels were dissected from the left side. The subcutaneous pouch was sutured to the right ventricle. The catheters, occluder tubing, flow probe, and pacing leads were tunneled through the chest wall and placed in a subcutaneous pouch at the base of the neck. The thoracotomy incision was closed, and the dogs allowed to recover.

Regional myocardial blood flow was determined by injecting 7- to 10-μm carbonized microspheres (Minnesota Mining and Manufacturing Co.) labeled with the γ-emitting radionuclides, 141Ce, 51Cr, 85Sr, 90Nb, and 45Sc, into the left atrium. Microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran. This stock solution was diluted further in 10% dextran so that 1.0 ml contained approximately 3 × 10⁶ microspheres. The microsphere solutions were mixed before injection by alternate agitation in an ultrasonic bath and a vortex agitator for at least 15 minutes. Blood flow measurements were made by injecting 1.0 ml of the microsphere suspension into the left atrial catheter over a 5-second interval. The catheter was flushed with 10 ml of normal saline over an additional 10 seconds. A reference sample of arterial blood was collected from the aortic catheter at a constant rate by means of a Harvard withdrawal pump. Collection began simultaneously with the microsphere injection and continued for 90 seconds. The withdrawal rate of the Harvard pump was carefully calibrated before and immediately after each study.

Varying degrees of myocardial bridging were modeled by totally occluding left circumflex coronary artery inflow during each cardiac cycle for systole (S) only, systole + 1/6 diastole (D), S + 1/3 D, and S + 1/2 D at a paced heart rate of 120 beats/min. During the course of each study, phasic and mean aortic and left atrial pressures, left circumflex coronary flow, and lead II of the electrocardiogram were recorded continuously. After several minutes, during which control data were recorded, one of the above occlusion interventions was initiated and continued for 3.5 minutes. After 2 minutes, 1.0 ml of microsphere suspension, labeled with a radionuclide, was injected into the left atrium. The reference blood sample was collected from the aortic catheter over the remaining 1.5 minutes. At the completion of blood collection, the occlusion intervention was discontinued and data recorded until baseline hemodynamics were attained. Hemodynamic and transmural myocardial blood flow data were obtained in this manner during each of the four conclusion interventions, as well as during a control period when no occlusion was taking place. The intervention sequence was selected randomly to eliminate data bias due to a specific intervention pattern.

At the conclusion of data collection, the animals were anesthetized with sodium thiamylal, 30 mg/kg, and fibrillated with 40 mEq potassium chloride, administered intravenously. The hearts were removed and fixed in 10% formalin for at least 3 days. After fixation, the atria, right ventricle, and large epicardial blood vessels were dissected from the left
ventricle and discarded. The left ventricle was sectioned into four transverse rings from base (ring 1) to apex (ring 4). Each ring was divided radially into seven anatomic regions corresponding to the anterior papillary muscle, anterior free wall, anterior and posterior septum, posterior free wall, posterior papillary muscle, and lateral free wall. Each region was subdivided into four transmural layers from epicardium (layer 1) to endocardium (layer 4). The individual tissue samples were weighed and placed in separate formalin-filled plastic vials for subsequent counting.

The γ activity for each radionuclide appearing in the reference blood and tissue samples was determined with a Packard model A5912 γ spectrophotometer (Packard Instruments Co.). Counts were accumulated in predetermined energy range "windows" selected to maximize activity from a given isotope while minimizing spillover from the other isotopes used in the study. The data were corrected for both background and Compton scatter. Total blood flow to each myocardial tissue sample (Qm) in milliliters per minute was calculated using the formula:

$$Q_m = Q_r - C_{nl}/C_r$$

where Q, is the reference blood flow (ml/min), Cm is the count activity in the myocardial tissue sample, and C is the total count activity in the reference blood sample. Total myocardial tissue sample blood flow was divided by the corresponding tissue sample weight and expressed as ml/min per g of tissue. The endocardial:epicardial blood flow ratio for a given anatomic region was obtained as the quotient of endocardial blood flow (layer 4) and epicardial flow (layer 1). For the purposes of this study, the ischemic area was defined as the lateral, posterior, and posterior papillary regions of rings 2 and 3.

Heart rate and phasic and mean aortic pressure, left atrial pressure, and left circumflex coronary flow were measured from the graphic output obtained at the time of microsphere injection. These data were averaged over several respiratory cycles prior to administration of microspheres and again following completion of reference blood sample collection.

A repeated measures analysis of variance was used to test for overall differences between the control period and the occluded interventions. If an overall difference was detected, a paired t-test was employed to compare the data for a single occluded intervention to its appropriate control value.

### Group 1

This portion of the study was designed to obtain accurate measurements of left circumflex coronary artery pressure distal to the balloon occluder during the course of the previously described interventions. Five dogs were premedicated with 20 mg of morphine sulfate and anesthetized with an intravenous dose of 80–100 mg of α-chloralose per kg (Fisher Scientific Corp.). The animals were intubated and maintained on an Emerson volume-cycled respirator throughout the study. A left thoracotomy was performed and an electromagnetic flow probe, a balloon occluder, a right ventricular bipolar pacing electrode, and aortic and left atrial catheters were placed as described for the dogs in group 1. In addition, a left circumflex coronary artery pressure catheter was inserted through the vessel wall distal to the balloon occluder. The coronary pressure catheter was constructed from a 6-cm length of polyethylene 60 tubing (Becton Dickinson and Co.) fitted over the cut distal portion of a 23-gauge hypodermic needle. The proximal end of the polyethylene tubing was connected directly to a Statham P23Db pressure transducer by means of a Luer-Lock adapter. The undamped natural frequency of the coronary catheter was tested and found to be greater than 30 cycles/sec (Glantz et al., 1979). The remaining instrumentation was arranged as described under group 1. A constant heart rate was maintained for each dog between 120 and 140 beats/min. Phasic aortic, left atrial, and peripheral coronary pressures, left circumflex coronary flow, and an ECG lead II tracing were recorded on an eight-channel direct-writing oscillograph and on an FM magnetic tape recorder during 2-minute occlusion interventions throughout systole only, S + 1/6 D, S + 1/3 D, and S + 1/2 D. At the completion of data recording, the animals were fibrillated with potassium chloride 40 mEq.

Ten-second segments of phasic analog data from the control period and during the final portion of each occlusion intervention were sampled at 5-nsec intervals and digitized with an IBM 1130/System 7 computer. The digitized data were displayed on an oscilloscope and 10 consecutive beats were indexed at pertinent points of the cardiac cycle. Subsequent computations yielded values for aortic systolic and diastolic pressure, coronary flow per beat, and phasic and mean peripheral coronary pressure during the inflow period.

### Results

#### Group 1

Figure 1 shows a representative tracing of the aortic pressure, left circumflex coronary blood flow, and ECG associated with each intervention carried out during the study. The rapid increase in coronary flow following each deflation of the balloon occluder demonstrates adequate phasic function of the occluder. The hemodynamic data obtained during each intervention are shown in Table 1. As previously noted, the heart was paced at 120 beats/min. Aortic and left atrial pressures during the control period and during the course of the occlusion interventions were not significantly different (P > 0.05). Left circumflex coronary flow was not statistically dif-

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Different from control values for occlusion durations of systole only or S + 1/6 D (P > 0.05). During the two prolonged occlusions, however, coronary flow was significantly reduced from the control values (P < 0.05). This reduction of mean coronary flow during the 3.5-minute course of occlusions lasting for either S + 1/3 D or S + 1/2 D was associated with a significant reactive hyperemic response when the occlusion intervention was terminated. A reactive hyperemic response was not observed following cessation of the lesser degrees of occlusion.

The transmural distribution of myocardial blood flow for the control period and during the occluded interventions is displayed in Figure 2. Blood flow and endo/epi blood flow ratio during the systole only and S + 1/6 D occlusions were not significantly different from control (P > 0.05). However, occlusions continuing through systole plus one-third diastole were associated with a significant flow reduction to the innermost subendocardial layer. This subendocardial flow reduction was even more marked during occlusion of S + 1/2 D, as shown in the lowermost curve of Figure 2. In this instance, mean flow as well as flow to transmural layers two through four was significantly reduced. Occlusion for both S + 1/3 D and S + 1/2 D was associated with a significant decrease in endo/epi ratio. None of the occlusion interventions elicited a flow reduction in the subepicardial layer (layer 1).

**Table 1** Hemodynamic Measurements: Group I

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Mean left atrial pressure (mm Hg)</th>
<th>Left circumflex coronary flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>115 ± 6</td>
<td>92 ± 6</td>
<td>6 ± 2</td>
<td>47.6 ± 10.4</td>
</tr>
<tr>
<td>Systole only</td>
<td>113 ± 7</td>
<td>90 ± 6</td>
<td>5 ± 1</td>
<td>39.7 ± 10.5</td>
</tr>
<tr>
<td>S+1/3D</td>
<td>117 ± 3</td>
<td>93 ± 4</td>
<td>5 ± 2</td>
<td>38.6 ± 9.5</td>
</tr>
<tr>
<td>S+1/2D</td>
<td>115 ± 5</td>
<td>91 ± 3</td>
<td>7 ± 1</td>
<td>32.2 ± 7.4*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.9 ± 4.4*</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.

* Those values significantly different from control (P < 0.05).
interventions described for the dogs in group 1. Representative phasic hemodynamic data are shown in Figure 3 for a control period and for occlusion of S + 1/2 D. During control, no significant aorta-to-coronary artery pressure gradient was observed. During the occlusion interventions, the magnitude and phasic pattern of distal coronary pressure was altered. A minimal decrease in distal pressure was observed during systole, followed by a more rapid decrease during the occluded portion of diastole. Following deflation of the balloon occluder, rapid coronary inflow occurred and the peripheral pressure increased to the systemic arterial pressure until the next occlusion was initiated. Qualitatively similar observations were made for the shorter duration occlusion interventions. The minimum diastolic coronary perfusion pressure decreased as the duration of occlusion increased; the time required for coronary perfusion pressure to reach its peak value following release of the occlusion increased as occlusion duration increased. Digitized data segments consisting of 10 consecutive cardiac cycles were analyzed during the control period and during occlusion of S + 1/2 D. The results of this analysis are shown in Table 2. The average cardiac cycle duration was 451 ± 27 msec. Throughout the occluded intervention, coronary inflow occurred only during the final 154 ± 9 msec of the diastolic interval. During this inflow period, the distal coronary pressure increased from a minimum value of 26 ± 5 mm Hg to a peak of 76 ± 9 mm Hg over an average of 113 ± 15 msec. The mean distal coronary pressure computed during the inflow period was 53 ± 10 mm Hg. The mean distal coronary pressure computed during the control period over the interval equivalent to the inflow period of the occluded intervention was found to be 82 ± 8 mm Hg and was significantly greater than during the occluded intervention (P < 0.01). Cor-
responding to this reduction in coronary perfusion pressure, the coronary flow per beat throughout the occluded intervention was significantly less than during the control period (P < 0.01).

Discussion

This study demonstrates that complete occlusion of the left circumflex coronary artery during S + 1/3 D and S + 1/2 D is associated with reduced coronary blood flow and a maldistribution of regional myocardial perfusion. The occurrence of a reactive hyperemic response following termination of these interventions, as well as the marked reduction in the ratio of endocardial to epicardial flow, indicates that myocardial ischemia was present during the intervention period. The reduction in myocardial flow cannot be explained on the basis of decreased myocardial oxygen requirements secondary to alteration of systemic hemodynamics. However, it is likely that the inflow time remaining in each cycle following release of the occlusion may have been insufficient to permit adequate perfusion.

In these studies, myocardial ischemia was produced by interrupting left circumflex coronary artery flow for the period of both systole and a significant portion of diastole. Systolic flow is normally 10-20% of total coronary flow, but this proportion can be increased in a variety of circumstances. When inflow occurs only during the period of systole, the volume of flow increases so that adequate flow is maintained in outer myocardial layers but the inner layers of the heart are underperfused (Rembert et al., 1978). In the present study, interruption of coronary flow during systole alone did not produce a significant decrease in myocardial flow, indicating that this relatively small reduction of coronary inflow could be compensated for during diastole. However, when coronary flow was interrupted for systole plus a significant portion of diastole, myocardial ischemia resulted. As the perfusion time remaining in each cycle is decreased, it would be expected that vasodilatory mechanisms act to maintain adequate myocardial flow. If a point of maximal vasodilation is reached and perfusion time is further reduced, myocardial ischemia could be produced. Although a critically reduced perfusion time may be implicated in the development of abnormal transmural blood flow distribution, it seems unlikely that this is the only mechanism responsible. In studies of myocardial blood flow in which the heart was paced at 250 beats/min, the blood flow distribution was normal in spite of the considerably reduced diastolic inflow time and higher flow/gram of tissue which occurs due to the increase in heart rate (Bache et al., 1977a). In those dogs, the diastolic inflow time per beat is shorter than in our dogs with occlusion of S + 1/2 D. Thus, in the situation in which coronary perfusion pressure is maintained at normal levels, the reduction in diastolic inflow time alone does not produce abnormal myocardial blood flow distribution.

Myocardial blood flow distribution is also a function of the coronary perfusion pressure. This pressure was measured in five open-chest dogs during the course of the various occlusion interventions; Table 2 shows the marked decrease in mean coronary artery pressure associated with occlusion for S + 1/2 D. This observation suggests that the subendocardial hypoperfusion was also related to the reduced coronary perfusion pressure. Buckberg et al. (1972) lowered aortic diastolic pressure in a series of open-chest dogs and observed that mean coronary and subendocardial regional flows were decreased. Similar results were reported by Bache et al. (1977b) following partial restriction of coronary artery flow in awake dogs. The precise decrease in coronary pressure necessary to produce maldistribution of regional flow is not known and is undoubtedly a function of multiple factors including the diastolic inflow time. In the present study, occlusion of coronary inflow for S + 1/2 D in the group 2 dogs was associated with a decrease in peripheral coronary pressure to a minimum value of 26 ± 5 mm Hg. This pressure is similar to that noted by both Buckberg et al. (1972) and Bache et al. (1977b) when endocardial hypoperfusion occurred. The progressive decrease in flow from epicardium to endocardium observed during this intervention may imply that a transmural gradient in the critical closing pressure is present and that increased intravascular pressures would be required to maintain perfusion in the deeper regions of the myocardium. It might thus be argued that, when coronary inflow was re-established with each beat and intracoronary pressure increased, the critical closing pressure of the epicardial layer was exceeded first and flow resumed to that region. Perfusion of the deeper layers followed as their respective critical closing pressures were exceeded.

It would seem logical that a muscle bridge would occlude coronary inflow only during systole and thus not produce a blood flow abnormality. In this study, subendocardial hypoperfusion was not demonstrated unless coronary inflow was interrupted for at least S + 1/3 D at a heart rate of 120 beats/min. Recently, Hill et al. (1981) reported coronary cineangiographic data from a patient with symptomatic myocardial bridging. Their data demonstrated lack of complete reopening of the bridged vessel until 50% of the diastolic interval had elapsed. Furthermore, intraoperative assessment of coronary flow showed delayed diastolic inflow; following supra-arterial myotomy, the flow delay resolved. Thus, the finding that may distinguish the rare patient with symptomatic muscle bridging is that the coronary artery is occluded during both systole and a significant portion of diastole. A mechanism to explain this delayed diastolic inflow is not readily apparent. However, Noble et al. (1976) noted an increased incidence of diffuse left ventricular hypertrophy in these patients. They proposed that diastolic relaxation of the bridged coronary segment
may be decreased and inflow subsequently delayed. The duration of diastolic delay necessary to produce a sufficient decrease in peripheral coronary pressure may be inversely related to heart rate. Clinical studies demonstrating evidence of ischemia in patients with myocardial bridging have done so at rates greater than 150 beats/min (Noble et al., 1976). Technical considerations precluded conducting the present study at such rates. However, the decreased coronary vascular resistance associated with increased heart rate will promote a more rapid reduction in peripheral coronary pressure during the time of occlusion and the decreased diastolic interval at this increased heart rate will allow less time for distal coronary pressure to be re-established when the occlusion is released.

In the present study, the characteristic systolic narrowing and delayed diastolic reopening of coronary arteries due to myocardial bridging was modeled by means of a 100% occlusion. Angiographic data have shown that symptomatic bridging, although associated with significant narrowing, does not generally produce complete occlusion (Noble et al., 1976). Despite this difference, we propose that the underlying mechanism remains unchanged, since significant narrowing of the coronary artery during systole and early diastole will result in a reduction of coronary inflow and a decrease in peripheral coronary pressure. After release of the obstruction, coronary flow is re-established and the coronary perfusion pressure rises. However, if the coronary pressure during the remaining portion of the diastolic interval is inadequate, subendocardial hypoperfusion will result.

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