Reductions in Regional Myocardial Function at Rest in Conscious Dogs With Chronically Reduced Regional Coronary Artery Pressure

John M. Canty Jr. and Francis J. Klocke

We have examined the temporal response of regional subendocardial function in conscious chronically instrumented dogs following implantation of a circumflex ameroid occluder. Collateralization was limited by ligation of epicardial anastomoses between the circumflex and adjacent coronary arteries at the time of instrumentation. Sonomicrometrically measured regional function in the circumflex coronary artery became depressed relative to that in the left anterior descending coronary artery bed under resting conditions with the onset of an aortic-circumflex pressure gradient of 15 ± 2.9 mm Hg (mean ± SEM). At the time of total ameroid occlusion, the ratio of circumflex to left anterior descending coronary artery function fell to 68 ± 8% of control, with mean circumflex coronary pressure decreasing to 60 ± 1.6 mm Hg. Following ameroid occlusion, distal coronary pressure increased, and circumflex function recovered towards control but remained depressed relative to that in the left anterior descending coronary artery for 2–4 weeks. Measurements of regional subendocardial perfusion suggested a dissociation between subendocardial flow and function prior to but not following coronary occlusion by the ameroid. We conclude that this model results in reductions in regional function that are relatively prolonged and are not readily attributable to subendocardial infarction or a critical reduction in resting coronary flow. The data suggest that functional adaptations in response to gradually developing coronary occlusion are more complex than those associated with acute reductions in coronary artery pressure and flow. (Circulation Research 1987;61(suppl II):II-107–II-116)

Regional myocardial mechanical function is closely coupled to coronary blood flow during acute reductions in coronary pressure produced by coronary artery constriction. When intrinsic autoregulatory mechanisms fail to maintain coronary flow at a constant level, subendocardial perfusion falls, and subendocardial function measured by segment shortening or wall thickening becomes depressed. These reductions in function are generally reversible as long as coronary flow is restored to normal levels before myocardial necrosis develops.

Measurements of regional myocardial performance and perfusion in patients with coronary artery disease suggest that the response to a chronic reduction in regional coronary artery pressure is more complex than that observed acutely in animal models of transient ischemia. St. John Sutton et al. have reported depressed anterior wall thickening distal to ≥50% diameter narrowing of the left anterior descending (LAD) or left main coronary artery in the absence of clinical evidence of myocardial infarction or angina. Local reductions in thallium exchange not associated with clinical evidence of myocardial ischemia, and presumably representing relative hypoperfusion of viable myocardium under resting conditions, have also been noted. Using positron emission tomography, Tillisch et al. have recently reported a pattern of depressed regional function with enhanced glucose metabolism relative to flow, which they suggest identifies areas of chronically but reversibly depressed function that improve following surgical revascularization. Also, measurements of regional coronary flow by inert gas washout have demonstrated reductions in resting flow distal to high-grade stenoses and in totally collateral-dependent myocardium. Collectively, these studies raise the possibility of a chronic state of reduced flow, reduced function, and altered metabolism in viable myocardium in patients with coronary artery disease.

The goal of the present study was to develop an animal model of chronically reduced regional coronary arterial pressure and to define the behavior of resting...
regional myocardial function in the model. Previous studies have reported that resting function in collateral-dependent myocardium of dogs is normal following gradual ameroid-induced coronary occlusion or repetitive brief total occlusion. Moreover, in the dog, vasodilator reserve quickly approaches normal levels following ameroid occlusion, and myocardial ischemia develops only in response to moderately severe stress. We attempted to limit collateral development in the dog during circumflex (LC) ameroid occlusion by ligating epicardial surface vessels connecting branches of the LC and adjacent coronary arteries at the time of ameroid implantation. Temporal responses in subendocardial function during and following ameroid occlusion were then compared in the collateral-dependent LC and normally perfused LAD regions.

**Materials and Methods**

**Chronic Preparation**

Ten adult mongrel dogs were studied (7 ameroid-instrumented and 3 sham-instrumented). Anesthesia was induced by sodium thiopental (20 mg/kg i.v.). Animals were then intubated, and a surgical plane of anesthesia was maintained using a nitrous oxide (~60%), oxygen (~40%), and halothane (~1–2%) mixture during mechanical ventilation. Under sterile conditions, a thoracotomy was performed in the fifth left intercostal space. Tygon catheters were placed into the descending aorta and left atrial appendage for microsphere injection. A Konigsberg micromonometer (Konigsberg Instruments P 6.5, Pasadena, Calif.) was placed into the left ventricular apex. Atrial pacing leads were sewn onto the left atrial appendage. The proximal circumflex artery was dissected free and instrumented with a hydraulic occluder. In 7 animals, an ameroid occluder (2.75 mm i.d.) was placed around the artery. In 3 sham-instrumented animals, the ameroid occluder was similarly placed but was removed prior to closing the chest. Teflon angioplastics (22 gauge) were connected to small-bore tubing and inserted into the distal LC artery and ascending aorta for chronic pressure measurement. The catheter system had a frequency response that was flat to at least 15 Hz and was, therefore, sufficient to measure phasic variations in aortic and left atrial coronary pressure at the heart rates encountered.

Regional myocardial function was measured with ultrasonic crystals placed to measure wall thickness (n = 9) and segment length (n = 4) in the LC and LAD free walls. One crystal of each wall thickness pair (2 mm o.d.) was placed tangentially into the subendocardium. The other (5 mm o.d.) was attached to a Dacron patch and sewn to the epicardium after locating the position of least-distance between the crystals while monitoring the signal on an oscilloscope. Subendocardial segment-length crystal pairs (2 mm o.d.) were oriented parallel to the endocardial fiber direction. Crystal location was confirmed at autopsy, with subendocardial crystals always located in the inner half of the left ventricular wall.

To limit collateral flow into the LC region, visible epicardial anastomoses arising between the LAD diagonal and LC marginal branches were ligated with epicardial sutures. The majority of these anastomoses arise near the apex and have been shown to be a major source of collateral vessel growth following gradual ameroid closure in the dog. In addition to connections between LAD and LC branches, the terminal right coronary artery was ligated in animals in which connections to distal circumflex branches were visible. Thus, in this model, collateral flow originated primarily from intramural anastomoses arising between the septal and posterior descending arteries.

At the conclusion of instrumentation, the chest was closed and the pneumothorax evacuated. Animals were given streptomycin (0.3 g) and procaine penicillin (300,000 units) parenterally for 3–5 days postoperatively. Catheters were flushed with saline and filled with heparin daily (10,000 U/ml for the circumflex artery catheter and 1,000 U/ml for other catheters). Aspirin (325 mg p.o.) was given on the fourth postoperative day and administered daily thereafter.

**Study Protocol**

Animals were brought to the laboratory 4–8 days postoperatively (±1 days, means ± SEM). Measurements of coronary hemodynamics and regional function were performed while the animals lay quietly on their right sides. Pressure gauges (Statham P23 TD, Gould Inc., Cleveland, Ohio) were zeroed at the level of the dorsal spine. The left ventricular micromonometer was adjusted using simultaneous measurements of aortic and left atrial pressures. Ultrasonic dimension signals were processed by a Triton Model 120 sonomicrometer (Triton Technology Inc, San Diego, Calif.).

Serial measurements of regional function and hemodynamics were performed at 1–3-day intervals. During each study, 3 15-second measurements of function under resting conditions were obtained over a 5–10-minute interval. Then, regional function was measured during a 1-minute total circumflex occlusion. The point of total ameroid occlusion was defined as the day on which LC pressure and function first remained unchanged during circumflex occlusion by the hydraulic occluder.

Regional myocardial perfusion was measured in 6 of the animals instrumented with an ameroid occluder. Up to 7 flow measurements were performed in individual animals using 15-μm microspheres labelled with the following γ-emitting nuclides: 153Gd, 7Co, 11In, 9Cr, 86Sr, 188Sn, 59Nb, or 46Sc. Microspheres were suspended in 10% dextran and 0.01% Tween-80. The suspension was placed in an ultrasonicator for at least 15 minutes, and vortex agitation prior to injection. Approximately 2–4·10⁶ microspheres were injected into the left atrium over a 10–15-second period. A reference blood sample was withdrawn at a constant rate (10 ml/min) from the descending aorta beginning prior to microsphere injection and continuing for 2 minutes. Flow measurements were performed at the point of total ameroid closure, at the terminal study, and at 1–2 points before and following ameroid closure. In 5 an-
mals, regional vasodilator reserve was assessed at the time of terminal study. Following an initial microsphere injection in the conscious state under resting conditions, anesthesia was induced using sodium thiopental and maintained with a halothane-nitrous oxide mixture. Coronary vasodilation was produced using carbocromen (7.5 mg/kg) injected into the left atrial cavity. Microsphere flow measurements were repeated 30 minutes after carbocromen injection. Following this, the animals were killed with a KCl overdose after ensuring a surgical plane of anesthesia, and hearts were removed and placed in 10% formalin for fixation.

Myocardial samples (16.5 ± 1.4 g) that included the crystal pairs were taken from the distal LC and LAD regions and cut into 4 transmural layers. Each sample was weighed, and activity was quantified using a Tracer-Northern sodium iodide detector. Activity of each isotope in a given sample was determined using a least-squares radionuclide separation technique. Regional flow was calculated using the reference sample technique.

Data Analysis

Hemodynamic data and sonomicrometer signals were recorded on a Gould 2800 W recorder at a paper speed of 100 mm/sec. All signals were digitized at a sampling rate of 200 Hz with a Data Translation DT 2801-A (Boston, Mass.) analog-to-digital converter interfaced to an IBM-PC computer. Hemodynamic measurements reported for resting conditions represent averages of the 3 separate 15-second measurements, each composed of at least 20 beats in sinus rhythm. End-diastole was defined as the point of onset of +dP/dt, and end-systole was defined as 20 msec prior to peak –dP/dt. Hemodynamic parameters examined included peak systolic and end-diastolic left ventricular pressure, mean aortic pressure, mean coronary and mean diastolic coronary pressure, and peak positive and negative dP/dt. End-diastolic dimensions and percent wall thickening and segment shortening were determined from the sonomicrometer signals.

Serial measurements of regional function were compared using the ratio of LC:LAD wall thickening (or segment shortening). The ratio of percent LC thickening (or shortening):percent LAD thickening (or shortening) on the first day of study was taken as the control value. Subsequent measurements of LC:LAD were expressed as percent of this control value. This procedure was intended to control for temporal variations in dimensions and/or global ventricular function, thereby facilitating the identification of changes in function in the collateral-dependent LC area relative to the reference LAD area.

In assessing temporal variations in regional myocardial flow, absolute flow in the LC endocardium (innermost left ventricular layer) was compared with that occurring simultaneously in the LAD endocardium and expressed as the LC:LAD ratio. Endocardial flow-function relations were determined for 4 time intervals: prior to ameroid occlusion (preocclusion), at ameroid occlusion, following ameroid occlusion (early postocclusion), and at the terminal study (late postocclusion). In 5 animals, flow was measured at the point of ameroid closure as well as at the time of the terminal study. Multiple flow measurements in individual animals before ameroid closure (n = 6) or between ameroid closure and the terminal study (n = 5) were averaged so that each animal was represented within a given group at these times only once.

All data were analyzed statistically using a one-way analysis of variance. Significant differences were determined using two-tailed paired t-tests and the Bonferroni correction for repeated measurements. Values reported represent the mean ± SEM.

Results

Postmortem examination of the myocardium never showed gross evidence of infarction in the LC subendocardium. However, fibrosis at the extreme tip of the posterior papillary muscle was sometimes noted. This fibrosis did not involve the areas between ultrasound crystals and was similar to that reported in previous studies using gradual ameroid occlusion.

Figure 1 shows analog records obtained from an ameroid-instrumented animal at 5 points during the experiment. The first panel (day 4) represents control data at the initial postoperative study to which subsequent measurements of function were normalized. The second panel (day 11) represents when the resting aortic-LC pressure gradient first exceeded 10 mm Hg. There is an increase in LAD function (LAD wall thickening and LAD segment shortening) with little change in LC function. Thus, when compared with control measurements, LC function is depressed relative to that in the LAD. The third panel (day 14) indicates the point of ameroid closure and is associated with a moderate reduction in mean distal coronary pressure to 60 mm Hg. At this time, LC function is reduced in absolute as well as relative terms, resulting in a further fall in LC function relative to that in the LAD. Following ameroid closure (fourth and fifth panels, days 25 and 42), both LC and LAD function increase over time, and the aortic-LC gradient diminishes. Thus, temporal changes in LC function in these animals reflect both absolute reductions in LC function with time and a failure of LC function to increase concomitantly with LAD function in the initial postinstrumentation period.

Figure 2 shows temporal measurements of normalized wall thickening and segment shortening (LC: LAD ratio expressed as percent of control) and aortic-coronary pressure gradient in 3 animals. The findings represent the variability observed in the total group studied. Measurements of ameroid-instrumented animals are shown in the two columns of panels on the left. Collateral-dependent circumflex regions developed reductions in the LC:LAD ratio with the onset of a resting aortic-LC pressure gradient >10 mm Hg. Relative LC function reached a nadir near the time of maximal resting pressure gradient and/or total ameroid occlusion. Following ameroid occlusion, the pressure gradient diminished over 3-4 weeks, and the LC:LAD
ratio returned toward control values. During this period, the LC:LAD ratio usually varied inversely with the magnitude of the resting aortic-LC pressure gradient; i.e., the ratio returned nearer to its control value when the resting gradient became less.

The response in sham-instrumented animals is shown in the column of panels on the right in Figure 2. In contrast with the collateral-dependent functional response, the LC:LAD function ratio remained at or above the control value for the full period of observation. The resting aortic-LC gradient was always <10 mm Hg. Figure 3 summarizes temporal relations of the LC:LAD function ratio for all animals. Data for each ameroid animal (filled circles) have been arranged in days prior to (negative) and following (positive) ameroid occlusion. At the point of ameroid occlusion (16±1.5 days following surgery), the LC:LAD ratio fell to 68±8 percent of its control value (p<0.05 vs. initial study) and was associated with a resting mean aortic-LC pressure gradient of 37.0±2.9 mm Hg (p<0.05 vs. initial study). Mean diastolic coronary pressure was 50±2.5 mm Hg (p<0.05 vs. initial study). Following ameroid occlusion, relative LC
function returned toward control values over 3 weeks as the resting pressure gradient diminished. Sham-instrumented animals (open circles) showed a pressure gradient <10 mm Hg and a possible trend for the LC:LAD ratio to increase with time.

Table 1 summarizes hemodynamic measurements in ameroid-instrumented animals at the time of initial study, the first day on which the aortic-LC gradient exceeded 10 mm Hg, the point of ameroid occlusion, approximately 10 days following ameroid occlusion, and at the time of terminal study (in 4 animals in which instrumentation functioned for an average of 45 ± 2.4 days). Except for LC pressure, the hemodynamic variables in Table 1 showed no significant changes at each point in time as compared with control.

Table 2 summarizes measurements of LC and LAD wall thickening at the same points mentioned above in ameroid-instrumented animals. At the time of initial study (6 ± 0.6 days following surgery), percent wall thickening was 22.4 ± 2.2 in the LC bed and 24.0 ± 1.4 in the LAD bed. At the onset of an aortic-LC gradient >10 mm Hg, percent wall thickening in the LC remained unchanged, but percent wall thickening in the LAD increased to 29.9 ± 5.7; i.e., there was an ~20% reduction below the control value in the LC:LAD ratio. At the time of ameroid occlusion, percent
LC wall thickening had fallen to $18.8 \pm 1.4$. Because of a further increase in percent LAD wall thickening, the LC:LAD ratio fell to $68 \pm 8\%$ of control at this time. Following total ameroid occlusion, both percent LC wall thickening and the LC:LAD ratio increased with time, in some cases reaching their original control values. Absolute values of end-diastolic LC and LAD wall thickness tended to decrease with time during the first 2-3 weeks following surgery. The changes in end-diastolic dimension were coupled with a trend toward increasing left ventricular end-diastolic pressure (Table 1), suggesting an increased end-diastolic volume and increasing use of the Frank-Starling mechanism.

Measurements of LC endocardial flow relative to the LAD and corresponding measurements of normalized LC:LAD wall thickening are shown in Figure 4. The dashed line represents the line of identity for reductions in the subendothelial flow and function ratios. Absolute endocardial and epicardial flows in the control zone (LAD) averaged $0.99 \pm 0.11$ and $0.65 \pm 0.05$ ml/min/g throughout the study ($n = 21$) and did not vary significantly with time ($p>0.05$, ANOVA). Up to and including the point of ameroid closure, LC flow showed little change relative to LAD flow despite moderately depressed LC function. Following ameroid occlusion, relative LC function continued to be depressed but a reduction in the LC:LAD flow ratio resulted in the flow-function point moving toward the line of identity. At the time of terminal study, both relative LC flow and function had increased in a parallel fashion. Inner flow:outer flow ratios did not vary significantly during the study in the LAD or LC regions and, in the LC area, averaged $1.29 \pm 0.05$.

Measurements of flow reserve at the terminal study using carbochromen showed endocardial flow to increase from $0.85 \pm 0.12$ to $1.14 \pm 0.09$ ml/min/g in the LC endocardium ($p=0.10$) and from $0.63 \pm 0.07$ to $1.97 \pm 0.16$ ml/min/g in the LC epicardium ($p<0.005$). Despite the absolute increases in flow, there was a fall in the LC inner flow:outer flow ratio from $1.34 \pm 0.11$ to $0.60 \pm 0.07$ ($p<0.001$). In the LAD region, endocardial flow increased from $0.81 \pm 0.12$ to $4.50 \pm 0.62$ ml/min/g, and epicardial flow increased from $0.53 \pm 0.04$ to $3.37 \pm 0.43$ ml/min/g. Thus, transmural flow reserve was present in both the LC and...
Figure 3. Temporal variations in regional circumflex function and resting aortic-LC gradient for ameroid-instrumented animals (filled circles) and sham-instrumented animals (open circles). Data for each animal have been grouped at 2-day intervals, with day zero defined as the point of total circumflex occlusion (15 ± 1.5 days following instrumentation). Numbers above each point represent number of animals contributing to the data point. As in data for individual ameroid-instrumented animals depicted in Figure 2, regional LC wall thickening became progressively depressed prior to total occlusion and returned toward control over subsequent 2–3-week period. Degree of resting wall thickening impairment was related to magnitude of resting aortic-LC pressure gradient. In sham-instrumented animals, in which the resting aortic-LC gradient remained <10 mm Hg, regional circumflex function remained at or above value obtained on initial day of study. (Data shown are for wall thickening in 2 of the 3 sham-instrumented animals and for segment shortening in the third animal.)

Discussion

This present study indicates that relative reductions in circumflex function occur under basal conditions during and following circumflex ameroid occlusion when collateral flow is limited by prior ligation of visible epicardial collaterals. The degree of reduction in collateral-dependent LC function relative to that in adjacent LAD myocardium varies with the magnitude of the aortic-LC pressure gradient. The reduction begins prior to total circumflex occlusion, reaches a nadir at the time of total occlusion, and returns toward control values over the next few weeks. Measurements of subendocardial perfusion suggest a dissociation between LC subendocardial flow and function prior to and at the point of ameroid closure; this dissociation subsequently resolves despite continuing functional impairment. The findings do not result from grossly identifiable myocardial infarction or temporal changes in systemic hemodynamics.

The use of the LC:LAD function ratio was intended to allow LC function to be evaluated over time independent of hemodynamic and/or temporal changes in overall left ventricular function following instrumentation. The major assumption was that function measured 4–8 days postoperation represented the normal ratio for any given animal and crystal pair. Although the ratio could have been affected by changes in function in the reference LAD zone in the absence of changes in LC function, the observed increases in percent LAD thickening in the early postoperative period presumably reflect, at least in part, a generalized Frank-Starling effect. It is possible that the lack of change in percent LC thickening during the same period represents the net effect of a depression in regional function counterbalanced by the Frank-Starling effect. The finding in sham-instrumented animals that the LC:LAD function remains at or above initially measured levels in the absence of progressive ameroid occlusion is compatible with this possibility. Small increases in the LC:LAD ratio in sham-instrumented animals over time may reflect recovery from surgical instrumentation, denervation hypersensitivity related to surgical manipulation of the circumflex artery.24 or
responses following intermittent episodes of ventricular tachycardia (which have been reported to occur commonly in the first several days after instrumentation). 13,14

The values of aortic-LC pressure gradients and distal coronary pressures in the present study are similar to the temporal changes in these parameters reported by Elliot et al. 15 during ameroid occlusion in conscious dogs. The finding of reduced LC function appears to contrast with results reported by others in canine models in which surface interarterial connections were not ligated. 13-15 Kumada et al. 11 compared function at 7 and 23 days following ameroid implantation and reported no significant change in LC segment shortening or wall thickening. Hill et al. 14 found no significant changes in resting segment shortening in animals studied up to 19 days following ameroid implantation. Both of these studies did, however, demonstrate moderate exercise-induced myocardial dysfunction. Yamamoto et al. 15 reported no changes in resting segment shortening following collateral development stimulated by multiple 2-minute coronary occlusions. In the present study, with collateral flow supplied primarily by the septal artery, relative LC wall thickening (LC:LAD ratio) was modestly but systematically reduced following ameroid implantation. The relative reductions in function began prior to ameroid occlusion, coinciding with the onset of a resting pressure gradient, and lasted for 2–4 weeks. The severity of functional impairment correlated with the magnitude of the resting aortic-LC pressure gradient, reaching a maximum near the time of ameroid occlusion. While subendocardial function was examined primarily using wall thickness measurements, segment shortening showed similar temporal responses in the animals in which it was measured (Figure 2). Our results suggest that adaptations to chronically reduced coronary pressure can involve reductions in resting regional function that parallel the magnitude of the pressure reduction.

Although LC function reductions appear to correlate with the resting aortic-LC pressure gradient, reductions in absolute levels of LC pressure were modest and seem unlikely to have resulted in acute myocardial ischemia. Our lowest mean coronary pressure averaged 60 mm Hg and occurred at the time of total ameroid occlusion (6 days). In contrast, during acute pressure reduction in unanesthetized dogs instrumented in a similar fashion, regional flow and function remained at control values until mean circumflex pressure fell below 40 mm Hg. This disparity argues against a primary reduction in resting flow as the basis of the reduced LC function at the time the animals were studied. The correlation of the aortic-LC pressure gradient with the degree of reduced function (Figures 2 and 3) could reflect a propensity of the collateral-dependent region to develop transient myocardial ischemia. Although vasodilator reserve was measured at only the terminal study, it is expected to have been inversely related to the resting aortic-LC pressure gradient at other points in the study. As the pressure

### Table 1. Hemodynamics in Ameroid-Instrumented Animals

<table>
<thead>
<tr>
<th>Day post-instrumentation</th>
<th>( P_{LV} )</th>
<th>( P_{LC} )</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Systolic (mm Hg)</td>
<td>End-diastolic (mm Hg)</td>
</tr>
<tr>
<td>6 ± 0.6</td>
<td>108 ± 4.6</td>
<td>62 ± 1.1</td>
</tr>
<tr>
<td>10 ± 1.4</td>
<td>117 ± 4.0</td>
<td>92 ± 2.0</td>
</tr>
<tr>
<td>16 ± 1.5</td>
<td>110 ± 4.9</td>
<td>82 ± 2.2</td>
</tr>
<tr>
<td>26 ± 1.4</td>
<td>110 ± 4.8</td>
<td>11 ± 3.6</td>
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<tr>
<td>45 ± 2.4</td>
<td>109 ± 7.0</td>
<td>8 ± 2.7</td>
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</table>

### Table 2. Regional Function in Ameroid-Instrumented Animals

<table>
<thead>
<tr>
<th>Day post-instrumentation</th>
<th>%LC WT</th>
<th>%LAD WT</th>
<th>ED LC WT</th>
<th>ED LAD WT</th>
<th>Normalized LC:LAD</th>
<th>LV ( \frac{dP}{dt} ) Maximum</th>
<th>LV ( \frac{dP}{dt} ) Minimum</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 ± 0.6</td>
<td>22.4 ± 2.2</td>
<td>24.0 ± 1.4</td>
<td>9.22 ± 0.34</td>
<td>8.55 ± 0.54</td>
<td>100</td>
<td>3,350 ± 390</td>
<td>3,017 ± 232</td>
<td>7</td>
</tr>
<tr>
<td>10 ± 1.4</td>
<td>22.2 ± 2.3</td>
<td>29.9 ± 5.7</td>
<td>9.05 ± 0.33</td>
<td>8.15 ± 0.48</td>
<td>80 ± 5*</td>
<td>3,493 ± 398</td>
<td>3,341 ± 255</td>
<td>7</td>
</tr>
<tr>
<td>16 ± 1.5</td>
<td>18.8 ± 1.4</td>
<td>30.6 ± 6.0</td>
<td>9.04 ± 0.44</td>
<td>8.09 ± 0.63</td>
<td>68 ± 5*</td>
<td>3,301 ± 402</td>
<td>3,101 ± 284</td>
<td>7</td>
</tr>
<tr>
<td>26 ± 1.4</td>
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<td>35.6 ± 7.1</td>
<td>8.36 ± 0.56</td>
<td>7.64 ± 0.80</td>
<td>83 ± 9</td>
<td>3,778 ± 360</td>
<td>3,306 ± 296</td>
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</tr>
<tr>
<td>45 ± 2.4</td>
<td>30.4 ± 3.4</td>
<td>23.5 ± 5.3</td>
<td>8.51 ± 0.77</td>
<td>8.14 ± 0.95</td>
<td>104 ± 21</td>
<td>2,793 ± 547</td>
<td>2,461 ± 439</td>
<td>4</td>
</tr>
</tbody>
</table>

\( P_{LV} \), left ventricular pressure; HR, heart rate; bpm, beats per minute; \( P_{AD} \), aortic pressure; \( P_{LC} \), circumflex pressure; \( P_{LC} \) gradient, aortic-circumflex pressure gradient; \( n \), number of animals. Mean ± SEM.

*p<0.05 vs. initial study at day 6.
Following ameroid occlusion, the resting coronary pressure level fell and the resting coronary pressure level fell, myocardial ischemia might have been provoked during relatively low levels of activity (when the animals were not monitored). If this hypothesis is correct, the functional reductions observed at rest may reflect postischemic dysfunction, i.e., "stunned" myocardium. Potential mechanisms producing acute transient reductions in flow in this model include not only demand-induced ischemia accompanying unmonitored exercise or excitement but also cyclical flow reductions due to platelet aggregation at the site of the ameroid occluder during the period of stenosis and prolonged periods of subtotal occlusion. In each of these situations, the recovery of regional function requires a substantial period following restoration of normal coronary flow. Each situation also appears to result in a dissociation between endocardial flow and endocardial function similar to that observed in our model up to the point of ameroid occlusion (Figure 4).

Following ameroid occlusion, resting coronary pressure gradually increased, and the aortic-LC pressure gradient decreased. Although resting LC function remained depressed, the LC:LAD flow ratio fell with an apparently closer coupling of endocardial flow and function until the time of terminal study. This flow-function relation is similar to that reported for changes in wall thickening and endocardial flow in response to acute transient myocardial ischemia. Since collateralization of the circumflex bed should improve progressively during the postocclusion period, the reduction in LC:LAD flow ratio is difficult to attribute to a further reduction in vasoconstrictor reserve. Because LC ameroid occlusion was complete, myocardial stunning related to cyclical changes in circumflex artery flow was no longer possible (although demand-induced stunning could have persisted). One possible, though speculative, explanation is that the reduction in LC:LAD flow ratio is a secondary effect of a reduction in resting LC function unrelated to myocardial stunning. Such an explanation would be consonant with studies suggesting reduced resting flow in viable myocardium in patients with coronary artery disease in the absence of signs of supply-demand imbalance, alterations in sympathetic responsiveness, and transient LC denervation related to fibrosis at the site of ameroid implantation.

In summary, these experiments indicate that moderate reductions in regional systolic function can occur under resting conditions in a chronic canine model of collateral-dependent myocardium. The regional coronary artery pressure associated with the reduction in function is higher than that at which regional dysfunction begins during acute reductions in coronary pressure in conscious animals. In addition, the close relation between subendocardial flow and function appears to be dissociated prior to ameroid occlusion and subsequently restored. These findings suggest that myocardial adjustments to chronic reductions in coronary pressure are more complex than adjustments to acute reductions.

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References

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