Altered Minimal Coronary Resistance to Antegrade Reflow After Chronic Coronary Artery Occlusion in Swine

D.M. Roth, F.C. White, and C.M. Bloor

We examined coronary pressure-flow relations after chronic coronary artery occlusion induced by placement of an ameroid occluder on the left circumflex coronary artery in swine. An acute open-chest procedure was performed in nine pigs 27 ± 2 days (mean ± SEM) after surgical placement of the ameroid occluder, and in eight nonoperated control pigs. Coronary vascular resistances were measured during maximal coronary vasodilation with adenosine. Minimal coronary resistance was assessed before and after cannulation and extracorporeal perfusion of the left circumflex coronary artery distal to the site of the ameroid occluder in pigs from the ameroid group and in a similar site in control pigs. Minimal coronary resistance to antegrade reflow in the left circumflex region was decreased significantly in ameroid pigs compared with control pigs (0.06 ± 0.01 vs. 0.26 ± 0.03 mm Hg • min • 100 g/ml, p < 0.001, respectively). Decreased minimal coronary vascular resistance was present transmurally in the left circumflex region of ameroid pigs. Altered vascular resistance occurred only in myocardium distal to the ameroid occluder since the nonoccluded left anterior descending region in ameroid pigs had minimal coronary resistance similar to that of the same region from control pigs (0.23 ± 0.03 vs. 0.19 ± 0.02 mm Hg • min • 100 g/ml). Thus altered minimal coronary vascular resistance occurs and probably reflects vascular proliferation and/or vascular alterations which result in an increased total cross-sectional area of the vasculature in the myocardium distal to the occlusion.


Revascularization of a region of myocardium beyond a coronary occlusion by an aorto-coronary bypass graft has been used clinically for several years for treating patients with coronary artery disease. However, investigators using animal models of gradual, chronic coronary occlusion have focused primarily on the growth and development of the coronary collateral circulation, which can supply nutritive blood flow to collateral-dependent myocardium beyond the site of coronary occlusion. Little information exists concerning antegrade reflow that has been established to myocardium distal to a chronic coronary artery occlusion in an animal model.

Flameng et al used bypass grafts to examine antegrade reflow distal to an ameroid occluder in dogs and did not find significant alterations in minimal coronary vascular resistance or maximal coronary blood flow in the collateral dependent myocardium. However, dogs may not be the appropriate species for investigating potential alterations in the myocardium and coronary vasculature distal to a chronic coronary occlusion. In contrast to humans, dogs possess an extensive innate coronary collateral circulation. Furthermore, the myocardial distal to the coronary occlusion in dogs is rapidly collateralized, resulting in little or no myocardial infarction and sufficient collateral blood flow to support the myocardium during exercise. Conversely, pigs possess a sparse innate collateral circulation and develop a limited collateral circulation in response to gradual coronary occlusion that is adequate to prevent severe myocardial infarction but is not capable of meeting the hyperemic demands of exercise even four months after placement of an ameroid occluder.

We hypothesized that maximal coronary blood flow and minimal coronary vascular resistance would
be altered in collateral dependent myocardium of swine as a result of chronic coronary artery occlusion when antegrade reflow was established distal to the occlusion. To test this hypothesis, we studied pigs subjected to gradual occlusion of the left circumflex coronary artery with an ameroid occluder and determined minimal coronary vascular resistance during adenosine infusion before and after recannulation and antegrade perfusion of the collateral-dependent left circumflex region.

Materials and Methods

Seventeen domestic Yorkshire swine (16 male, 1 female) weighing 43 ± 1 kg (mean ± SEM) were used in this study. Nine pigs were subjected to a surgical procedure to produce gradual occlusion of the left circumflex coronary artery. Eight nonoperated pigs served as control animals.

Surgery for Chronic Coronary Artery Occlusion

Nine pigs were sedated with ketamine (25 mg/kg), atropine (0.05 mg/kg i.m.), and sodium thiamylal (20 mg/kg i.v.). The pigs were intubated and maintained on 1–2% halothane anesthesia during an aseptic surgical procedure. A left thoracotomy was performed at the fifth intercostal space. The pericardium was opened, and the proximal left circumflex coronary artery was dissected free of surrounding tissue for a length of 1–1.5 cm. A metal-encased ameroid occluder with a 2.5–3.0-mm lumen (K-G Ulrich, Montreal, Quebec, Canada) was placed around the dissected artery. An ameroid occluder was chosen with the proper luminal dimensions to provide a close but nonconstrictive fit to the artery. The pericardium and chest were closed, and the pigs were allowed to recover. An acute open-chest experiment was performed approximately 27 days (27 ± 2 days, range 23–44 days) after placement of the ameroid occluder.

Experimental Procedure

Acute open-chest experiments were conducted in all 17 swine. The pigs were sedated as described previously for the chronic surgeries, intubated, and maintained on 1–2% halothane throughout the acute experiment. The pigs were mechanically ventilated with an Ohio intermittent positive pressure respirator (Cincinnati, Ohio) using 100% O₂. The respirator was adjusted to maintain proper arterial pH, Pco₂, and Po₂ greater than 100 mm Hg. Rectal temperature was maintained above 37°C. Polyethylene catheters were placed in both carotid arteries, the common iliac artery and a peripheral leg vein for microsphere injections and adenosine infusion, respectively. A left thoracotomy was performed. Silastic catheters were placed in the left and right atria for microsphere injections and adenosine infusion, respectively. These catheters also were used for intermittent monitoring of atrial pressures. The left circumflex coronary artery (LCX) was dissected free of tissue and adhesions just distal to the site of the ameroid occluder in preoperated animals and in a similar region in control animals.

At this time infusion of adenosine (1 mg/kg/min) into the right atrium was started. This dose of adenosine has been used previously to produce maximal coronary vasodilation in swine. The descending thoracic aorta was constricted with a fluid-filled occlusion cuff to maintain coronary perfusion pressure during the subsequent blood flow measurements. The degree of aortic occlusion was adjusted until mean aortic pressure was greater than 100 mm Hg or the maximum mean aortic pressure if 100 mm Hg was not attainable. Radiolabeled microspheres (approximately 6 million 15-μm spheres dissolved in 10% Dextran-0.01% Tween 80, New England Nuclear, Boston, Massachusetts) were injected into the left atrium to measure left anterior descending (LAD), LCX, and collateral regional blood flows and minimal resistances. A reference blood sample was withdrawn at a rate of 7.75 ml/min from the carotid artery.

The LCX then was cannulated just distal to the ameroid occluder or at a similar site in control animals. Extracorporeal perfusion of this region of myocardium was established. A bolus of lidocaine (20–60 mg) was given before the cannulation. The perfusion system, modified from the method of Nathan and Feigl, consisted of a blood-withdrawal catheter placed in the common iliac artery, an adenosine infusion port, a microsphere injection port with a stir bar agitator, a servo-controlled Cole Parmer Model 7520-25 variable flow pump (Chicago, Illinois), a Windkessel apparatus, a reference blood withdrawal port, and a Biotronex 3/16" extracorporeal flow transducer (Kensington, Maryland) (Figure 1). The pump supplying blood flow to the LCX was controlled by an analog feedback circuit to maintain a constant coronary perfusion pressure. The coronary cannula (luminal diameter, 1 mm) was equipped with a side arm 17 mm from the cannula.

\[ \text{FIGURE 1. Schematic diagram of the acute experimental preparation and perfusion system, which depicts a heart from an ameroid pig. A similar preparation was used in control pigs.} \]
tip for monitoring coronary pressure. The mean resistance of the cannula system over the range of coronary flows used in the study was 0.03 mm Hg · min/ml. All values for coronary perfusion pressures used in the study were corrected for this pressure drop. Blood coagulation in the perfusion system was prevented by infusion of 20,000 units sodium heparin IV and maintained by infusion of 10,000 units every hour. During extracorporeal perfusion mean coronary pressure was maintained at 90–100 mm Hg. Following a 5–10 minute equilibration with extracorporeal perfusion, adenosine (4 mg/min) was infused into the coronary perfusion circuit. Simultaneously, adenosine was infused into the systemic circulation through a peripheral leg vein at a dose of (1 mg/kg/min). Systemic administration of adenosine was performed in conjunction with intracoronary adenosine infusion to 1) decrease aortic blood pressure and coronary collateral driving pressure (i.e., aortic blood pressure) and minimize the effect of collateral blood flow upon our measurements and 2) decrease left ventricular pressure and ventricular wall stress minimizing the effect of extravascular compressive forces upon the transmural distribution of coronary blood flow during our measurements. In preliminary experiments an intracoronary dose of adenosine of 1.5 to 2.5 mg/min produced maximal coronary vasodilation. We arbitrarily performed our experiments with 4 mg/min of adenosine to assure maximal coronary vasodilation. Radiolabeled microspheres (approximately $5 \times 10^3$ spheres) were injected into the coronary perfusion line at this point to determine maximal coronary blood flow and minimal coronary resistance. A reference blood sample was withdrawn simultaneously at a rate of 1.95 ml/min from the coronary perfusion circuit.

With the coronary vasculature still maximally dilated with adenosine mean coronary perfusion pressure was reduced in 25 mm Hg increments at 30-second intervals until zero coronary flow was achieved. The coronary pressure at zero flow (PzF) was noted and the perfusion pressure was returned to 90–100 mm Hg. The adenosine infusions then were stopped. Twenty to thirty minutes after adenosine infusion coronary blood flow in the LCX region was recorded in six ameroid pigs and four control pigs with the flow transducer on-line in the perfusion circuit. Coronary blood flows also were recorded with the flow transducer in seven ameroid pigs and four control pigs during the initial equilibration period after LCX cannulation and before adenosine infusion.

Trypan blue dye was injected into the coronary cannula to delineate the region of myocardium perfused by the extracorporeal system. The hearts were excised and placed in 10% buffered formalin for 24–48 hours before postmortem analysis. The region surrounding the ameroid occluder in ameroid pigs was removed and examined to determine the status of the LCX lumen. The lumen was closed completely in eight of nine ameroid pigs. Collateral blood flow and resistance were not calculated in the animal with a partially opened lumen since some forward flow in the LCX region probably existed at the time of the collateral flow determinations.

Similar experiments also were performed in three dogs to corroborate previous studies of coronary resistance in canine preparations. Gradual occlusion of the proximal left circumflex coronary artery by placement of an ameroid occluder was performed in a similar manner as described for pigs. The dogs, all male (32–39 kg) were tested during the acute procedure with LCX coronary cannulation distal to the occluder as described previously for the pig at 24, 26, and 27 days following initial surgery.

**Determinations of Coronary Blood Flows and Resistances**

Coronary blood flows were determined using radiolabeled microspheres and coronary flow transducer recordings. The radiolabels included $^{4}$Sc, $^{85}$Nb, $^{103}$Ru, $^{113}$Sn, $^{51}$Cr, $^{110}$In, and $^{141}$Ce. Myocardial blood flows were determined according to methods of Heymann et al in the following manner: Hearts from all animals were cut into five transverse rings 1–1.5 cm thick from base to apex. The region of the LCX perfused during the acute cannulation experiment and delineated by the trypan blue dye was cut from the various rings and weighed. The perfused LCX region weighed $26 \pm 2$ and $33 \pm 3$ g in pigs from the ameroid and control groups, respectively. The LCX region perfused after cannulation averaged $24 \pm 1\%$ of the entire left ventricle for all pigs. One transmural section of this region from each of the two most basal rings weighing 2–4 g and lying at least 10 mm inside the dye border of the region was removed and divided into subendocardial, midmyocardial, and subepicardial layers. Similarly, two transmural sections of myocardium perfused by the LAD were removed from the second and third most basal rings of the heart and divided into three layers. Transmural blood flows presented in the results represent averages of the individual layers of myocardium. Samples of myocardium and reference blood samples were analyzed for the quantity and energy level of gamma radiation with a Packard Autogamma Spectrometer (model 5912, Downers Grove, Illinois). Radiation counts were corrected for overlap and background activity with solution of simultaneous equations using a matrix inversion technique. Blood flows are expressed in milliliters per minute per 100 g. Blood flows obtained from flow transducer recordings represent mean blood flow divided by the weight of the dye delineated perfused region. Blood flows in the LCX region of ameroid occluded animals were corrected for the presence of myocardial infarcts. The extent of infarct was determined by histological analysis using a quantitative morphometric point counting technique. Myocardial infarct in the LCX region aver-
Table 1. Hemodynamic Indexes at Maximal Coronary Vasodilation With Adenosine During Determinations of Maximal Coronary Blood Flow

<table>
<thead>
<tr>
<th>Group</th>
<th>Before LCX cannulation</th>
<th>After LCX cannulation</th>
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<tbody>
<tr>
<td></td>
<td>Control (n = 8)</td>
<td>Ameroid (n = 9)</td>
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<tr>
<td></td>
<td>Control (n = 8)</td>
<td>Ameroid (n = 9)</td>
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<td></td>
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<td></td>
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<tr>
<td>Mean aortic blood pressure (mm Hg)</td>
<td>100 ± 4</td>
<td>75 ± 7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 5</td>
<td>74 ± 6</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>16 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>7 ± 2</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>Mean coronary pressure (mm Hg)</td>
<td>96 ± 2</td>
<td>89 ± 3</td>
</tr>
<tr>
<td>Pressure zero flow (mm Hg)</td>
<td>18 ± 2</td>
<td>18 ± 2</td>
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Values represent mean ± SEM. *p<0.05, significant difference ameroid group versus control group.

Results

Hemodynamics

Hemodynamic parameters during the myocardial blood flow and coronary resistance determinations are presented in Table 1. During maximal coronary blood flow and minimal coronary resistance measurement before LCX cannulation, mean aortic blood pressure was significantly lower in the ameroid pigs compared with control pigs (p<0.05). Mean aortic blood pressure also was significantly lower during maximal coronary blood flow measurements after LCX cannulation in ameroid pigs compared with control animals (p<0.05). No other significant differences in hemodynamic parameters were observed during either maximal coronary blood flow determination.

During the measurement of maximal antegrade blood flow to the LCX region of myocardium after cannulation of the LCX coronary artery a pressure gradient of 42 ± 3 mm Hg and 49 ± 4 mm Hg existed between the extracorporeal perfused LCX region of myocardium and the LAD and right coronary regions of the left ventricle in control and ameroid pigs, respectively. Despite this pressure gradient collateral blood flows to the LAD region of myocardium measured by microspheres injected into the LCX perfusion system were 4 ± 3 ml/min/100 g and 35 ± 15 ml/min/100 g in control and ameroid pigs. The collateral blood flows to the LAD region were only 1.2% and 2.6% of the maximal coronary blood flows measured in the LCX region of myocardium of control and ameroid pigs and were not significantly different.

Maximal Coronary Blood Flow and Minimal Coronary Resistance

Figure 2 shows maximal coronary blood flow and minimal coronary resistance obtained during maximal vasodilation with adenosine before cannulation of the LCX coronary artery in ameroid and control pigs. Minimal coronary resistances in the LAD regions of pigs from both groups were not significantly different. Values for minimal coronary resistance in the LAD region were 0.19 ± 0.02 and 0.23 ± 0.03 CRU for pigs from the control and ameroid groups respectively. Minimal coronary collateral resistance in the LCX region of ameroid pigs was significantly higher (p<0.05) than the minimal coronary resistance in the LCX region of control pigs (1.57 ± 0.35 vs. 0.27 ± 0.03 CRU, respectively).
In control pigs, minimal coronary resistance in the LAD region was significantly less than that observed in the LCX region (p<0.005).

Following cannulation and antegrade perfusion of the LCX coronary artery distal to the ameroid occluder in ameroid pigs and in a similar location in control pigs coronary blood flows before coronary vasodilation with adenosine were 136 ± 19 ml/min/100 g and 202 ± 27 ml/min/100 g in eight control pigs and seven ameroid pigs, respectively. These values were not significantly different. Coronary pressures during these flow meter measurements were similar in both groups, 99 ± 2 and 99 ± 1 mm Hg.

Figure 3 shows maximal coronary blood flow and minimal coronary resistance in the maximally vasodilated LCX region after cannulation of the LCX coronary artery in both groups. Maximal coronary blood flow increased significantly (p<0.001) and minimal coronary resistance decreased significantly during antegrade reflow to myocardium beyond the ameroid occluder compared with flows and resistances observed after LCX cannulation in control pigs. Maximal coronary blood flows in the LCX region were 330 ± 38 and 1340 ± 140 ml/min/100 g for control and ameroid pigs, respectively. Minimal coronary resistances in the LCX region after cannulation and extracorporeal perfusion were 0.26 ± 0.03 and 0.06 ± 0.01 CRU for control and ameroid pigs, respectively.

The transmural distribution of maximal coronary blood flow and minimal coronary resistance in the LCX region following cannulation and antegrade reperfusion are shown in Figure 4. Minimal coronary resistance was reduced significantly (p<0.001) in all three layers of myocardium distal to the ameroid occluder when compared with minimal coronary resistance in the LCX region of control pigs. Minimal coronary resistances in the subendocardium, midmyocardium, and subepicardium of the LCX region of ameroid pigs were 0.07 ± 0.01, 0.05 ± 0.01, and 0.07 ± 0.01 CRU, respectively.

Pressure-flow relations derived from flow transducer recordings of antegrade reflow in the cannulated LCX region during maximal coronary vasodilation are plotted for the control and ameroid pigs in Figure 5. When coronary perfusion pressure of 100 mm Hg is substituted into the regression equation for the two groups minimal coronary resistances of 0.25 and 0.08 CRU are obtained for the control and ameroid groups, respectively.

Twenty minutes after pressure-flow determinations with adenosine coronary blood flow had returned to 125 ± 21 ml/min/100 g and 178 ± 26 ml/min/100 g in four control pigs and six ameroid pigs, respectively. Coronary pressures during these measurements were 96 ± 3 mm Hg in control pigs and 98 ± 2 mm Hg in pigs from the ameroid group.
CONTROL GROUP

Roth et al
Vascular Resistance After Coronary Occlusion

AMEROID GROUP

Canine Data

In the three dogs studied after gradual LCX occlusion, minimal coronary resistance during adenosine infusion was 0.15 ± 0.01 CRU in the LAD region of myocardium. Minimal coronary collateral resistance in the LCX region was 0.66 ± 0.18 CRU in these animals. In two dogs studied after successful cannulation of the LCX coronary artery distal to the ameroid occluder, minimal coronary resistance to antegrade reflow was 0.16 and 0.12 CRU.

Discussion

Placement of an ameroid occluder around a coronary artery results in gradual occlusion of the artery over 2–3 weeks and produces a collateral-dependent region of myocardium beyond the site of occlusion.2,3 In this study, we hypothesized that maximal coronary blood flow and minimal coronary vascular resistance would be altered in myocardium of swine when antegrade reflow was established distal to the coronary occlusion. The results show that during maximal coronary vasodilation with adenosine minimal coronary resistance to antegrade reflow beyond the site of coronary occlusion is reduced significantly compared with the minimal coronary resistance of normal myocardium. The altered minimal coronary vascular resistance occurred transmurally in the subendocardial, midmyocardial, and subepicardial layers of the heart. Furthermore, this altered coronary vascular resistance is specific to the region of myocardium supplied by the occluded artery since no significant change in coronary vascular resistance was noted in the LAD perfused region of myocardium of the ameroid pigs compared with control animals.

Coronary blood flow was measured in our study by both the radiolabeled microsphere technique16 and by an on-line blood flow transducer. Coronary vascular resistances derived by these two methods were very comparable. All measurements of maximal coronary blood flow and minimal coronary resistance were made during systemic and intracoronary infusion of adenosine. Adenosine has been used by other investigators to achieve maximal coronary vasodilation in swine during coronary hemodynamic measurements.15 Vascular resistance was computed using one of two formulas. After cannulation of the LCX, coronary resistance to antegrade reflow was calculated using the difference in mean coronary pressure and pressure zero flow (Pzf) for that artery as an approximation of coronary perfusion pressure.20 Back pressure on a coronary artery when forward flow ceases (Pzf) has been shown to be approximately 15 mm Hg for the LAD coronary artery in pigs.15–21 Pzf in our control pigs averaged 18 mm Hg for the LCX coronary artery. This higher value of Pzf for the LCX in pigs may be due to the higher innate collateral blood flow in this region of myocardium compared with the LAD region.7 The dependence of Pzf on coronary collateral flow was a necessary consideration in our study since collateral development does occur in pigs in response to chronic coronary occlusion with an ameroid occluder.19 To alleviate this

FIGURE 4. Transmural distribution of maximal coronary blood flow and minimal coronary resistance following cannulation and antegrade perfusion of the left circumflex region. Endo, subendocardium; Mid, midmyocardium; Epi, subepicardium. Values represent mean±SEM. **p<0.001, significant difference ameroid group versus control group.

FIGURE 5. Plot of pressure-flow relations following cannulation and antegrade perfusion of the left circumflex region during maximal coronary vasodilation. Linear regressions were derived from 29 data pairs from nine pigs in the ameroid group and 28 data pairs from eight pigs in the control group. MCR, minimal coronary resistance at a perfusion pressure of 100 mm Hg in coronary resistance units of mm Hg • min • 100 g/ml.

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problem adenosine was given both systemically and intracoronary during blood flow measurements and determination of Pzf. This lowered the LAD and right coronary artery perfusion pressures that serve as coronary collateral perfusion pressure, resulting in a Pzf in ameroid pigs that nearly equaled the Pzf in control pigs. Minimal coronary resistances in this study were similar regardless of whether right atrial pressures or left atrial pressures (an estimate of left ventricular end-diastolic pressure) were used in the calculation of coronary perfusion pressure.14

Systemic infusion of adenosine during the measurement of maximal blood flow in the extracorporeal perfused LCX region created a pressure gradient between the LCX region of myocardium (mean coronary pressure approximately 90 mm Hg) and the LAD and right coronary regions of myocardium that were perfused with a mean aortic pressure of approximately 40–50 mm Hg (Table 1). Despite this pressure gradient little collateral blood flow occurred between the extracorporeal perfused LCX region and the LAD region of myocardium during the measurement of maximal antegrade blood flow to the LCX region. This result most likely was due to the sparse coronary collateral circulation of the pigs in the control group and the combination of the high collateral vascular resistance and low minimal coronary vascular resistance in the LCX region of pigs from the ameroid group.

Before cannulation of the LCX, coronary vascular resistances in control pigs and LAD and collateral resistances in pigs from the ameroid group were calculated with mean aortic pressure – mean left atrial pressure representing coronary perfusion pressure since no direct measure of Pzf was obtained. Mean left atrial pressure has been used as an estimate of left ventricular end-diastolic pressure previously in calculating coronary perfusion pressure.13 Also, this derivation of coronary perfusion pressure results in minimal coronary resistances for the LCX region of control pigs that are similar to resistances estimated with the coronary cannula using mean coronary pressure – Pzf. Although Pzf is known to exceed left ventricular end-diastolic pressure by a few millimeters of mercury15,20 this difference would not alter the conclusions of our study. Since adenosine was being infused systemically during the measurements of minimal coronary vascular resistances, the aorta was constrained with an occlusion cuff to maintain aortic pressure above 100 mm Hg or the maximal mean aortic pressure if 100 mm Hg was not achievable. The mean aortic blood pressure attained under these conditions during the aortic constriction was significantly lower in the ameroid pigs compared with the control pigs (Table 1). This result suggests myocardial function in the partially collateral dependent left ventricle of ameroid pigs was depressed compared with the control pigs during these blood flow determinations. Marzilli and coworkers22 have reported that changes in myocardial contractile function of the heart can affect coronary blood flow measurements. In their study, coronary blood flow increased 29% when contractile performance of the myocardium was reduced 100% by intracoronary lidocaine infusion. Although myocardial function may have been depressed in ameroid pigs compared with control pigs in our study, we do not think the degree of myocardial depression was large enough to significantly alter our results.

The values obtained for minimal coronary vascular resistance in the control pigs from our study are similar to resistances measured by other investigators in swine. Most et al,21 using adenosine-induced maximal vasodilation of the LAD region of myocardium in swine, found minimal coronary resistance to be 0.25 mm Hg • min • 100 g/ml. White et al12 arrived at a similar value for minimal coronary resistance of the LCX region of myocardium in maximally exercising pigs during adenosine infusion. Furthermore, similar values for minimal coronary resistance in the LCX region of our control animals were obtained from measurements made with 1) microspheres before LCX cannulation, 2) microspheres during extracorporeal perfusion of the LCX, and 3) the flow transducer on line in the perfusion system. Our results also showed that the minimal coronary resistance was greater in the LAD region compared with the LCX region of control pigs. Minimal coronary resistance in these two regions of myocardium have not been compared simultaneously in previous studies in swine. Also, maximal coronary blood flow measured during intracoronary adenosine infusion, did not favor the subepicardial layers of myocardium in either control or ameroid pigs as has been reported previously by some investigators.23 The lack of this preferential subepicardial blood flow redistribution in our study was most likely due to the simultaneous administration of adenosine into the systemic circulation. This procedure tended to decrease left ventricular pressure and myocardial wall stress thus reducing the effect of extravascular compressive forces upon the transmural distribution of coronary blood flow.14

Minimal coronary vascular resistances measured in the LCX region of Ameroid pigs, when antegrade reflow was established distal to the site of the ameroid occluder, were 73% and 70% lower than minimal coronary resistances measured in the LCX region of control pigs and the LAD region of ameroid pigs, respectively. This decrease in minimal coronary vascular resistance in the LCX region was not dependent on full closure of the ameroid occluder since one ameroid pig, who had partial opening of the coronary lumen at autopsy, had a minimal coronary resistance in the LCX region similar to the mean for the ameroid group (0.06 CRU vs. 0.06 ± 0.01 CRU, respectively). Also, the change in minimal coronary resistance of this region, although fast in onset (apparent 23 days following...
Coronary vascular resistances have not been examined previously in swine following chronic coronary vessel occlusion. This phenomenon of reduced minimal coronary vascular resistance distal to a coronary occlusion has not been observed previously in dogs.\(^{4,24}\) Flameng et al\(^4\) showed that the coronary vascular reserve measured during dipyridamole vasodilation was not altered significantly in dogs following a bypass graft around a coronary occlusion induced by an ameroid occluder. Scheel and coworkers\(^{24}\) also have reported increased minimal vascular resistance to antegrade reflow in dogs 5 months after placement of an ameroid occluder on the LCX coronary artery. Our values for minimal coronary resistance and minimal collateral resistance in the dog are consistent with values reported previously by Schaper et al.\(^{25}\) Also, in agreement with Flameng's coronary bypass studies,\(^4\) our data in two dogs with antegrade reflow distal to the site of occlusion showed no change in minimal coronary vascular resistance.

In Flameng's study,\(^4\) dogs that showed signs of myocardial infarction actually had decreased coronary vascular reserve in myocardium distal to the ameroid occluder, which suggests an increased coronary vascular resistance in these animals. The pigs in our study demonstrated a wide range of percentage of myocardial infarction (0.3% to 34%) yet all pigs showed a significantly decreased minimal coronary resistance. Three pigs with relatively little infarct (less than 1% of the region at risk), had a mean minimal coronary resistance of 0.7 ± 0.02 CRU. While the two pigs with the largest percentage of infarcts (34% and 27% of the region at risk) had minimal coronary resistance very similar to pigs with less infarct (0.08 and 0.07 CRU before correction for infarct and 0.05 CRU for both pigs after correction for infarct). As described in the methods, blood flow in myocardium with >5% infarct was adjusted for the presence of infarct.\(^{10,19}\) The infarct correction did not significantly alter the blood flow values and coronary resistance calculations in our study since minimal coronary resistance in the LCX region of ameroid pigs was 0.07 ± 0.01 CRU before infarct correction and 0.06 ± 0.01 CRU after infarct correction. We conclude from these data that the presence of myocardial infarction had little effect on minimal coronary resistance in viable myocardium from the LCX region of pigs subjected to coronary occlusion. Furthermore, it appears from these data that myocardial infarction was not a primary cause of the significantly decreased minimal coronary resistance in the LCX region of our pigs.

Differences between the pig and the dog in alterations in pressure-flow characteristics of myocardium distal to a chronic coronary occlusion may be due to differences in the collateral circulations of the two species. The pig, in contrast to the dog, possesses a sparse innate collateral circulation consisting of a fine anastomotic network of endomural vessels similar to coronary collateral vessels in humans.\(^2\) In response to chronic coronary occlusion, the pig develops a limited collateral circulation that prevents severe myocardial infarction but cannot maintain normal myocardial perfusion during exercise or pharmacological vasodilation.\(^{8,10,19}\) In dogs, coronary collateral vessel development after gradual coronary occlusion results in little or no myocardial infarction and sufficient collateral blood flow to maintain coronary blood flow during exercise.\(^6\) Schaper et al\(^{25}\) have shown that minimal coronary collateral resistance, a measure of collateral vascular reserve, is approximately 0.65 CRU in the LCX region of dogs 4 weeks after placement of an ameroid occluder around the LCX. Minimal collateral resistance decreased to 0.48 CRU 8 weeks after placement of the occluder in their study indicating further development of the collateral circulation and an increase in collateral vascular reserve. Pigs in our study had a minimal collateral resistance of 1.57 CRU 3–4 weeks after placement of the occluder. Furthermore, the pigs studied 6 weeks after placement of the occluder had a minimal collateral resistance of 1.54 CRU, indicating little further development of the coronary collateral circulation. Thus, the pig develops a less extensive coronary collateral circulation, has less collateral vascular reserve, and has increased potential for myocardial ischemia as a result of chronic coronary artery occlusion compared with the dog. This increased potential for myocardial ischemia in the collateral dependent myocardium of pigs may be related to the minimal coronary resistance changes we observed in our animals.

The increased maximal coronary blood flow and decreased minimal coronary resistance in the LCX region distal to the ameroid occluder resulted in a leftward shift of the coronary pressure-flow relation of this region (Figure 5). In accordance with Hoffman's work,\(^{26}\) such a shift would indicate an increased coronary vascular reserve of the myocardium if basal blood flow requirements of the myocardium have not changed dramatically. Since myocardial blood flows were not significantly different between our control and ameroid pigs after coronary cannulation and before maximal vasodilation, an increased coronary vascular reserve appears to have occurred in the collateral dependent region of myocardium.

Hoffman\(^{26}\) also states that maximal coronary blood flow at a given perfusion pressure is a function of the total cross-sectional area of the coronary resistance vessels in that region. The significantly increased maximal coronary blood flow in the collateral-dependent LCX region of pigs in our study strongly suggests vascular proliferation and/or that vascular alterations have occurred in the
LCX region resulting in an increased total cross-sectional area of the coronary vasculature. It is conceivable that vascular proliferation, which is known to occur in the coronary collateral circulation in response to the hemodynamic and ischemic stress of coronary occlusion, also may occur in collateral dependent myocardium. Furthermore, our laboratory previously has shown histological changes in arterioles in collateral dependent myocardium after placement of an aneurysm occluder. Changes included arteriolar dilation, medial hyperplasia, adventitial fibrosis, elastin fiber disarray, and medial mucoid degeneration. Despite the vascular changes in the collateral dependent myocardium indicated by our results, coronary blood flow measurements in the LCX region before intracoronary adenosine showed that this region has resting vascular tone that returns after cessation of adenosine infusion. This result indicates that the LCX region of myocardium from ameboïd pigs can autoregulate blood flow. However, the autoregulatory capacity of this region in comparison with normal myocardium is unknown.

Humans possess a large variation in the extent of collateralization of the myocardium. However, some humans do possess a limited coronary collateral circulation as indicated by the presence of myocardial ischemia and dysfunction during exercise. Whether alterations we observed in the myocardium of pigs as a result of chronic coronary occlusion can occur in the human is not known. Studies in which coronary reflow was examined during vasodilation in humans after aorto-coronary bypass surgery have not shown evidence of altered coronary blood flow or coronary vascular resistance in the reflow region. However, variations in coronary collateralization, degree of coronary stenosis, and patency of the bypass graft may complicate documentation of the changes in coronary pressure-flow characteristics that were observed in our study. Furthermore, maximal coronary vasodilation, necessary for the measurement of minimal coronary resistance, may not have been attained in these studies since others have shown maximal coronary blood flow in humans to be greater than the flows they reported. More studies employing maximal coronary vasodilation after establishment of coronary reflow would be necessary to answer whether minimal coronary resistance can be decreased and coronary vascular reserve increased in human myocardium following chronic myocardial ischemia.

In conclusion, our results support our hypothesis that chronic occlusion of the LCX coronary artery in swine alters maximal coronary blood flow and minimal coronary vascular resistance. The study shows that in a species with a limited coronary collateral circulation and little coronary collateral reserve, vascular alterations occur after gradual coronary artery occlusion, which decreases minimal coronary resistance in the region of the heart at risk of myocardial ischemia.

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References


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Altered minimal coronary resistance to antegrade reflow after chronic coronary artery occlusion in swine.

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