Effect of Cyclooxygenase Blockade on Blood Flow Through Well-Developed Coronary Collateral Vessels

John Altman, Daniel Dulas, and Robert J. Bache

Collateral vessels that develop after coronary artery occlusion demonstrate perivascular inflammation, subintimal hyperplasia, and endothelial proliferation. This study was performed to test the hypothesis that these abnormalities are associated with evidence for increased production of vasodilator prostaglandins. Eight dogs were studied 4–6 months after occlusion of the anterior descending coronary artery had been performed to stimulate collateral vessel growth. At the time of study, the anterior descending coronary artery was cannulated at the site of occlusion to allow measurement of retrograde blood flow as an index of interarterial collateral flow. Injection of radioactive microspheres during the retrograde flow collection allowed determination of continuing tissue flow in the collateral-dependent zone as an index of intramural microvascular collateral flow. Retrograde and tissue flows were measured before and 20 minutes after 5 mg/kg i.v. indomethacin, a dose that caused 95±3% inhibition of the coronary vasodilation in response to a 500 μg intracoronary bolus of arachidonic acid. Heart rate and mean aortic pressure were not significantly altered by indomethacin, and blood flow to the normally perfused myocardial region was not changed by administration of indomethacin. However, indomethacin caused a 40±7% decrease in retrograde flow (p<0.01), and microvascular collateral flow to the dependent myocardium decreased by 20±10% (p<0.05). These data indicate that, unlike the normal coronary circulation, well-developed coronary collateral vessels are under the tonic influence of vasodilator prostaglandins. (Circulation Research 1992;70:1091-1098)

KEY WORDS • coronary vessels • coronary occlusion • myocardial blood flow • prostaglandins • indomethacin

Although the coronary vessels are responsive to locally produced vasoactive derivatives of arachidonic acid,¹ most evidence does not support an important role for prostaglandins in regulation of coronary blood flow during physiological conditions. Thus, Owen et al² and Harlan et al³ reported that cyclooxygenase blockade with indomethacin did not alter baseline blood flow or the increase in flow that occurred during reactive hyperemia or in response to the increased myocardial oxygen demands produced by isoproterenol in open-chest dogs. Similarly, indomethacin did not alter coronary blood flow or myocardial oxygen extraction in intact awake dogs either at rest or during graded treadmill exercise.⁴ These reports thus fail to support a substantial role for products of cyclooxygenase metabolism in regulation of the normal coronary circulation.

Collateral vessels that develop in response to coronary artery occlusion have a well-developed muscular media and are capable of active vasomotion, which may modulate blood flow to the dependent myocardium.⁵,⁶ Unlike normal arterial vessels, however, ultrastructural examination of these collateral vessels has demonstrated perivascular inflammation, monocyte adherence to the endothelium, subintimal hyperplasia, and endothelial proliferation.⁷,⁸ Although these histological abnormalities are most prominent during collateral growth early after coronary occlusion, Schaper et al⁹ found endothelial proliferation in collateral vessels 1 year after coronary occlusion. Because these histological abnormalities may be associated with elevated local prostaglandin production,¹⁰ this study was performed to examine the effect of cyclooxygenase blockade on coronary collateral blood flow.

Materials and Methods

These studies were performed in accordance with the position of the American Heart Association on research animal use adopted November 11, 1984, and under the supervision of the Animal Care Committee of the University of Minnesota. Two groups of adult mongrel dogs were studied. Group 1 consisted of five unoccluded dogs that were used to document the degree of cyclooxygenase blockade that could be achieved by measuring the response of coronary blood flow to intracoronary arachidonic acid before and after treatment with
indomethacin. Group 2 consisted of eight dogs with chronic coronary artery occlusion that were used to examine the effect of cyclooxygenase blockade on coronary collateral blood flow.

**Group 1**

Five adult mongrel dogs of either sex were anesthetized with sodium pentobarbital (30–35 mg/kg i.v.), intubated, and ventilated with a respirator (Harvard Apparatus, South Natick, Mass.) with room air and supplemental oxygen. Under sterile conditions, a left thoracotomy was performed in the fifth intercostal space. A heparin-saline–filled polyvinyl catheter (3.0 mm o.d.) was introduced into the left internal thoracic artery and advanced into the ascending aorta. The pericardium was opened, and a heparin-filled catheter was introduced into the left ventricle near the apical dimple. The proximal left circumflex coronary artery was mobilized and a 5-MHz Doppler flowmeter probe was fitted around the artery. A heparin-filled Silastic catheter (0.3 mm o.d.) was inserted into the circumflex artery distal to the flowmeter probe.10 The pericardium was loosely closed, the catheters and electrical leads were tunneled subcutaneously to exit in the interscapular area, and the chest was closed in layers. Catheters and electrical leads were protected by a nylon vest the animals had been trained to wear. Catheters were flushed with heparin-saline daily to maintain patency.

Studies were performed seven to 10 days after surgery. Aortic and left ventricular pressures were measured with Statham P23ID pressure transducers. Circumflex blood flow was measured with a Doppler flowmeter (Craig Hartley, Houston, Tex.). Data were recorded on an eight-channel recorder (Coulbourn Instruments Inc., Lehigh Valley, Pa.). Injections of arachidonic acid or its vehicle were made into the coronary artery, and the flow responses were observed. Arachidonic acid was dissolved in a solution of 10% ethanol in 100 mM Na₂CO₃ under nitrogen. This solution was diluted with isotonic saline to a final concentration of 1 mg/ml and used within 3 hours after preparation. The response to intracoronary arachidonic acid or vehicle (0.5 ml) was observed in triplicate at 5-minute intervals to ensure that a consistent response was achieved. Indomethacin (5 mg/kg) was then administered as an intravenous bolus. Twenty minutes after the administration of indomethacin, the hemodynamic and coronary flow responses to intracoronary arachidonic acid and its vehicle were again observed. The response to vehicle was subtracted from the arachidonic acid response, and the excess flow produced by arachidonic acid was compared with the corresponding measurement obtained after administration of indomethacin.

**Group 2**

**Development of collateral vessels.** Collateral vessel development was induced by catheter embolization of the left anterior descending coronary artery with a hollow plug in eight adult mongrel dogs as previously described.6 Animals were anesthetized with sodium pentobarbital (25 mg/kg i.v.), intubated, and ventilated with a respirator. The right carotid artery was isolated under sterile surgical conditions. After administration of heparin sodium (6,000 units i.v.), an 8F Judkins right coronary artery catheter was introduced into the left coronary ostium and directed toward the anterior descending artery. A 0.014-in. angioplasty guide wire was passed through the catheter into the distal anterior descending artery. Nitroglycerin (100 μg i.c.) was given. The coronary catheter was removed without disturbing the guide wire, and a hollow stainless-steel plug (2.3–2.7 mm o.d., 1.1 mm i.d., 4 mm in length) was pushed along the guide wire with a length of flanged PE-90 tubing until the plug was firmly wedged in the coronary artery. The guide wire was removed, and the position and patency of the plug were confirmed by fluoroscopy during intracoronary injection of 5 ml of 60% diatrizoate meglumine.

**Surgical preparation.** The animals were returned to the laboratory 4–6 months after coronary embolization, premedicated with morphine sulfate (1 mg/kg s.c.), anesthetized with α-chloralose (100 mg/kg i.v. followed by 10 mg/kg per hour), intubated, and ventilated with a respirator. Supplemental oxygen was used to maintain arterial Po₂ within the physiological range. Two 7F NIH catheters were introduced into the femoral arteries and positioned in the ascending aorta for blood sampling and for pressure monitoring. A similar catheter was introduced into the left carotid artery and advanced into the left ventricle for pressure measurement. A left thoracotomy was performed in the fifth intercostal space. A pneumatic cuff occluder was fitted around the descending thoracic aorta to allow control of proximal aortic pressure. The heart was suspended in a pericardial cradle and a polyvinyl chloride catheter (3.0 mm o.d.) was inserted into the left atrium through the atrial appendage. The coronary artery plug was located by palpation, and the anterior descending artery was dissected free for 1.0–1.5 cm proximal and distal to the plug. After administration of sodium heparin (200 units/kg i.v. followed by 1,000 units/hr), the artery was occluded proximally, and a longitudinal arteriotomy was performed. The plug was extracted, and the artery was allowed to bleed freely to dislodge any residual thrombus. The artery was then cannulated with a thin-wall stainless-steel cannula (4.0 mm o.d.). Resistance of the coronary cannula determined from the pressure drop produced by passing measured flows of blood through the cannula was 0.097 mm Hg/ml per minute of flow. Pressure at the cannula tip was measured with a 23-gauge tube incorporated into the wall of the cannula.

**Myocardial blood flow.** Myocardial blood flow was measured with 15-μm-diameter microspheres labeled with 125I, 53Cr, 85Sr, 85Nb, 85Sc, or 113Ce (NEN Co., Boston, Mass.; and 3M Co., St. Paul, Minn.). Microspheres were obtained as 1.0 mCi in 10 ml of 10% low molecular weight dextran. Microspheres were agitated in an ultrasonic bath for at least 10 minutes before injection. For each intervention, 3 × 10⁶ microspheres were injected into the left atrium, and a reference sample of arterial blood was withdrawn from the aortic catheter at a constant rate of 15 ml/min with a peristaltic pump. Reference sampling was begun at the time of microsphere injection and continued for 90 seconds.

**Experimental protocol.** Aortic, left ventricular, and coronary cannula pressures were measured with Statham P23ID pressure transducers. Left ventricular pressure was recorded at normal and high gain for measurement of end-diastolic pressure. Left ventricular
dP/dt was obtained by electronic differentiation of the pressure signal. Data were recorded on an eight-channel direct-writing recorder (Coulbourn Instruments). Interarterial collateral blood flow was measured by collecting retrograde flow from the coronary artery cannula into a graduated cylinder for 30-second intervals while the cannula tip was maintained at the level of the heart. The level of the cannula tip was maintained constant throughout the study. Control measurements of retrograde blood flow were repeated until consistent measured collections were obtained. Measurements were thereafter performed in triplicate, and the results were averaged. To assess microvascular collateral flow that continued during diversion of coronary artery cannula flow, an injection of microspheres was administered to six of the animals during control conditions simultaneously with a retrograde flow collection.

After completion of the control measurements, indomethacin was administered as a single intravenous bolus dose of 5 mg/kg. Hemodynamic variables were recorded continuously, and retrograde blood flow collections were performed in duplicate at 20 minutes after the administration of indomethacin. A second injection of microspheres was administered simultaneously with the final retrograde flow collection 20 minutes after the administration of indomethacin. In five of the animals, hemodynamic measurements and retrograde flow collections were repeated 60 minutes after indomethacin administration.

To allow determination of total collateral tissue flow, the shadow technique of Patterson and Kirk\(^\text{11}\) was used to delineate the collateral-dependent myocardial region. For this procedure, microspheres were administered into the left atrium while the coronary cannula was perfused with nonradioactive arterial blood from a pressurized reservoir. Cannula tip pressure was maintained 10 mm Hg above mean aortic pressure during the microsphere injection. In this way, the myocardium distal to the site of occlusion was perfused with nonradioactive blood to distinguish it from the remainder of the heart, which was marked with microsphere-containing blood.

**Tissue preparation.** The heart was excised and fixed in 10% buffered formalin, and the left ventricle was divided into four transverse rings parallel to the mitral valve ring. The rings were then sectioned radially into 16 segments, which were divided into epicardial and endocardial halves. The resultant specimens were weighed on an analytical balance and placed into vials for counting. Myocardial and blood reference samples were counted in a gamma spectrometer with a multichannel analyzer (model 5912, Packard Instrument Co., Inc., Downers Grove, Ill.) at window settings corresponding to the peak energies of each radionuclide. The activity in each window was corrected for background and overlapping counts between isotopes with a digital computer. Blood flow to each myocardial specimen \((Q_m)\) was computed using the formula \(Q_m = Q_c \times C_m / C_c\), where \(Q_c\) is reference blood flow rate (in milliliters per minute), \(C_m\) is counts per minute of myocardial specimen, and \(C_c\) is counts per minute of reference blood specimen. Blood flows were expressed as milliliters per minute per gram of myocardium.

**Data analysis.** Total flow to the collateral tissue was computed as the sum of absolute blood flow to all myocardial samples in the collateral-dependent region as identified by the shadow technique. Heart rate and pressures were measured directly from the strip-chart recordings. Hemodynamic data were analyzed using analysis of variance for repeated measures. A value of \(p < 0.05\) was required for statistical significance. Comparisons of retrograde blood flows and microsphere flows between control and intervention were analyzed with the Wilcoxon signed rank test and independent \(t\) test. All data are expressed as mean±SEM.

**Results**

**Group 1**

The response to intracoronary bolus injection of arachidonic acid is shown in Table 1. Administration of arachidonic acid resulted in no change in heart rate or aortic pressure but produced a 75±8% peak increase in coronary artery blood flow. The coronary vasodilation produced by arachidonic acid was brief in duration, with flow returning to the control level within 1–2 minutes. Indomethacin resulted in a nonsignificant increase in mean aortic pressure with a significant decrease of heart rate from 141 to 125 beats per minute \((p<0.05)\). Indomethacin produced 95±3% inhibition of the coronary vasodilation produced by arachidonic acid \((p<0.01)\).

**Group 2**

**Hemodynamic data.** Hemodynamic measurements before and after administration of indomethacin are shown in Table 2. Mean aortic pressure tended to increase and heart rate tended to decrease after indomethacin administration, but these changes did not achieve statistical significance. Left ventricular end-diastolic pressure was not significantly changed after the administration of indomethacin. Left ventricular dP/dt was slightly decreased after indomethacin administration \((p<0.02)\). Distal coronary pressure with the cannula closed tended to decrease after indomethacin administration, although this did not achieve statistical significance. However, the tendency for distal coronary pressure to decrease in conjunction with a trend toward increased aortic pressure resulted in a 65% increase in the aortic to coronary pressure gradient after the administration of indomethacin \((p<0.03)\).

**Retrograde blood flow.** Retrograde flow measurements from the cannulated left anterior descending coronary artery are shown in Figure 1. During control
conditions, retrograde flow ranged from 11 to 71 ml/min (mean, 41±7 ml/min). Twenty minutes after indomethacin administration, retrograde blood flow was decreased in every animal studied (mean decrease, 40±7%; *p<0.01). In five animals, retrograde blood flow measurements were monitored for 1 hour after the administration of indomethacin. In these animals, retrograde flow remained depressed throughout the 60-minute observation period after the administration of indomethacin, so that retrograde flow 60 minutes after indomethacin administration (29±9 ml/min) was not different from retrograde flow 20 minutes after indomethacin administration (31±9 ml/min).

Collateral zone tissue flow. Myocardial blood flow measurements obtained with the shadow technique demonstrated a sharp boundary between collateral-dependent and adjacent normally perfused myocardium. Collateral-dependent myocardium ranged from 12 to 29 g (mean, 18±2 g). Total left ventricular mass ranged from 99 to 161 g (mean, 125±9 g). Collateral-dependent myocardium represented an average of 15±2% of the left ventricle.

Tissue blood flows measured with microspheres are shown in Table 3. During control conditions, blood flow in the normal zone was 0.78±0.08 ml/min per gram, and flow to the subendocardium (ENDO) was significantly greater than flow to the subepicardium (EPI) (ENDO/EPI=1.29±0.08). Normal zone blood flow and the ENDOK/EPI ratio were not altered by indomethacin. Blood flows to the collateral-dependent myocardium shown in Table 3 and Figure 2 were made with the coronary cannula open to atmospheric pressure, so they represent continuing microvascular collateral flow not diverted during the retrograde flow collection. As shown in Figure 2, there was considerable variability in blood flow to the collateral-dependent region during control conditions with the cannula open; animals appeared to fall into two groups of three having relatively high flows (mean, 0.71±0.06 ml/min per gram) and three having relatively low flows (mean, 0.41±0.02 ml/min per gram). Of all measured variables, only mean aortic pressure was different between these two groups; values were 106±5 mm Hg in the high flow group and 87±1 mm Hg in the low flow group (*p<0.02). Indomethacin decreased mean tissue flow in the collateral-dependent region by 20±10% (*p<0.05); the decrease in flow was more prominent in the high flow group, so that flows in all animals were tightly grouped after the administration of indomethacin. No hemodynamic change could be found that might explain the more prominent decrease in response to indomethacin in the high flow group. Other measures of collateral function, including retrograde flow and the pressure gradient from aorta to coronary artery with the cannula closed, were not different between the two groups, suggesting that the response to indomethacin was not determined by the degree of collateral development. Total collateral blood flow obtained as the sum of retrograde flow and collateral zone tissue flow is shown in Table 4. Total collateral blood flow decreased 31% after cyclooxygenase blockade (*p<0.01).

Discussion

Cyclooxygenase blockade with indomethacin caused no significant change in blood flow to normally perfused myocardium. This is in agreement with previous studies in normal hearts which have found little evidence that prostaglandins participate in the control of coronary blood flow during physiological conditions.2-4 In contrast to the lack of effect on perfusion of normal myocardium, indomethacin caused a substantial decrease of collateral blood flow. This finding suggests that the prostaglandins exert tonic vasodilator activity on coronary collateral vessels. This new finding, as well as the method for determination of collateral blood flow, will be discussed in detail.

**TABLE 2. Hemodynamic Data for Eight Dogs With Chronic Coronary Artery Occlusion (Group 2) During Control Conditions and After Administration of Indomethacin**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>LV end-diastolic pressure (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>Mean coronary pressure (mm Hg)</th>
<th>Aortic-coronary pressure gradient (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>138±11</td>
<td>95±4</td>
<td>5±1</td>
<td>2300±200</td>
<td>78±5</td>
<td>17±2</td>
</tr>
<tr>
<td>INDO</td>
<td>130±12</td>
<td>99±4</td>
<td>7±2</td>
<td>2000±200*</td>
<td>71±5</td>
<td>28±3*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. bpm, Beats per minute; LV, left ventricular; INDO, after administration of 5 mg/kg i.v. indomethacin.

*p<0.05 in comparison with control.

**FIGURE 1. Plot showing individual responses (open circles) of retrograde blood from the anterior descending coronary cannula of eight dogs during control conditions (CON) and 20 minutes after administration of 5 mg/kg i.v. indomethacin (INDO). Mean±SEM blood flow is indicated by solid circle with bars. *p<0.01 vs. CON.**
In the present study, opening the coronary cannula to atmospheric pressure did not abolish tissue flow in the collateral-dependent region. For this reason both retrograde and tissue flows were measured to account for total collateral flow. Continuing tissue flow during retrograde diversion indicates that some collaterals enter the recipient vessel distal to a site of significant resistance, so that antegrade flow encounters less resistance than flow back into the arterial cannula. Collaterals may develop at several levels in the coronary arterial vasculature; at each level the fraction of flow diverted when the cannula is opened is determined by the relative ratio of antegrade versus retrograde resistance.\[12\] Scheel et al\[13\] reported that embolizing the collateral-dependent myocardium with microspheres up to 50 \(\mu\)m in diameter increased retrograde flow, whereas embolization with 80-\(\mu\)m microspheres decreased retrograde flow, suggesting that the smallest collaterals entered recipient vessels between 50 and 80 \(\mu\)m in diameter. Downey et al\[14\] found that in well-collateralized hearts 84-\(\mu\)m microspheres embolized into the distal vasculature were dislodged by a subsequent period of retrograde flow, indicating that some collaterals entered recipient vessels less than 84 \(\mu\)m in diameter. In normal canine hearts, Harrison et al\[15\] determined that mean stem pressure at the origin of the collateral vessels was within 7 mm Hg of aortic pressure, whereas collaterals arising from vessels with a pressure of 45 mm Hg could account for no more than 25% of total collateral flow. In the present study, antegrade tissue flow constituted approximately 20% of total collateral flow. If these data can be extrapolated to the normal hearts studied by Harrison et al, the microsphere flow could be accounted for by collaterals originating from arterial vessels with pressures of approximately 45 mm Hg. Thus, approximately half of the vascular resistance would be proximal to the origin of these microvascular collaterals. Since Chilian et al\[16\] demonstrated that approximately 45% of coronary resistance resides in vessels larger than 100 \(\mu\)m in diameter, the findings are consistent with the previous reports suggesting that the smallest collateral vessels are likely to be in the range of 80 \(\mu\)m in diameter.\[13,14\] However, the increased flow in the well-collateralized heart would increase the pressure in the recipient vessel, so that it is likely that collaterals larger than this could result in sufficient pressure to perfuse the distal vascular bed. In addition, the resistance offered by the cannula would cause increased pressure in the recipient artery and encourage antegrade flow. However, cannula resistance was relatively low and would have caused only a minimal increase in pressure in the recipient artery. It should be noted that residual flow within the shadow region was uniform and not preferentially delivered to the border region. This indicates that even the smallest collateral vessels entered the recipient arterial system sufficiently proximal to cause uniform distribution of flow in the recipient vascular bed.
Since the resistance to collateral blood flow includes not only the collateral vessels but also the coronary arterial segment proximal to the origin of the collateral vessels, epicardial artery constriction could have contributed to the observed decrease in collateral flow in response to indomethacin. However, Lane and Bove, using quantitative angiography in anesthetized dogs, found that indomethacin (5 mg/kg i.v.) caused no change in the cross-sectional area of normal coronary artery segments. This finding indicates that the decreased collateral flow observed in the present study could not be ascribed to indomethacin-induced vasoconstriction of coronary arteries proximal to the origin of the collateral vessels. Collateral flow can also be influenced by changes in normal zone flow. Thus, agents that cause vasodilation of resistance vessels in normal myocardial regions increase the pressure drop across the proximal coronary artery segment, thereby decreasing the pressure available at the origin of the collateral vessels. In the present study, blood flow in the normal region did not change in response to indomethacin administration. Thus, indomethacin did not produce changes in either the coronary arteries or the coronary resistance vessels in the normal myocardium that would be expected to cause a decrease in collateral blood flow.

The observed decrease in tissue blood flow in the collateral-dependent region in response to indomethacin could have resulted from vasoconstriction of either the collateral vessels or the resistance vessels distal to the site of entry of the collateral channels into the recipient arterial vasculature. Indomethacin did not cause generalized constriction of the coronary resistance vessels, since blood flow in the normal myocardium was not decreased. However, small-vessel responsiveness may be altered in vascular beds perfused by collateral vessels. Thus, Sellke et al found that endothelium-dependent dilation was depressed in coronary arterioles chronically perfused through collateral vessels. It is possible that an abnormality of endothelium-derived vasodilator prostaglandins could also exist in small vessels perfused through collateral channels.

Although no previous studies are available examining the effect of cyclooxygenase blockade on well-developed coronary collateral vessels, several investigators have reported the effects of these agents on blood flow through native collateral vessels after acute coronary artery occlusion. These studies demonstrated that indomethacin, ibuprofen, or flurbiprofen did not alter blood flow through native collateral vessels after acute coronary occlusion. Capurro et al reported that aspirin (600 mg i.v.) caused a small but significant increase in blood flow to the subepicardium of the acutely ischemic region between 5 minutes and 4 hours after coronary occlusion in open-chest dogs. However, small increases in collateral flow have been shown to occur spontaneously during the first hours after acute coronary artery occlusion in the dog, so that it is unclear whether the small increase in collateral flow was the result of a drug effect. Thus, the available data do not document a consistent effect of cyclooxygenase blockade on the native collateral vessels that exist at the time of acute coronary occlusion.

Collateral vasoconstriction produced by indomethacin is likely mediated through inhibition of local prostanoid production. Vascular prostaglandin production is concentrated in the endothelial cells. In ultrastructural studies of well-developed canine collateral vessels examined 8–52 weeks after ameroid collar formation, Schaper et al found increased numbers of endothelial cells per unit inner vascular space when compared with normal vessels. The present study suggests that this endothelial cell proliferation is associated with increased production of vasodilator prostaglandins in the collateral vessels. Prostacyclin is the principal enzymatically generated prostaglandin in vascular endothelial cells and is a potent vasodilator of coronary arteries and resistance vessels. Several investigators have examined the effect of prostacyclin on blood flow through the rudimentary collateral vessels that exist at the time of acute coronary artery occlusion, but the results are conflicting. Jugdutt et al found that prostacyclin reduced infarct size in awake dogs subjected to acute coronary artery occlusion and that this effect was associated with an increase in blood flow to the acutely ischemic myocardium. Smith et al also found that prostacyclin exerted a protective effect on acutely ischemic myocardium, but this effect occurred with no change in collateral blood flow. In contrast to the equivocal response of native collateral vessels, Scholtholt et al using isolated perfused canine hearts 5 weeks after ameroid constrictor implantation, found that prostacyclin (100 μg/min i.c.) caused a 50% decrease in transcollateral resistance. This finding indicates that moderately well-developed coronary collateral vessels are responsive to the vasodilator effects of prostacyclin and is consonant with the concept expressed in the present study that interruption of endogenous prostacyclin production decreases tonic vasodilator activity.

In addition to causing inhibition of prostacyclin production, cyclooxygenase blockade has potential for increasing leukotriene production by diversion of arachidonic acid from prostaglandin synthesis into the lipoxygenase pathway. Arachidonic acid is cleaved by 5-lipoxygenase to form 5-HPETE, which is then converted to numerous products including leukotriene C4 and D4, which are potent coronary vasoconstrictors. Leukotriene production was first demonstrated in leukocytes but has been shown to occur in rabbit hearts and in isolated human and canine epicardial coronary artery segments. The potential for indomethacin-induced leukotriene production thus exists in coronary vessels, but Lane and Bove demonstrated that normal canine epicardial arteries do not undergo vasoconstriction in response to indomethacin. Developing collateral vessels show perivascular leukocyte infiltration, which could enhance local leukotriene production, but these abnormalities are evident principally during early collateral development and are absent after 8 weeks of collateral growth. The present study was carried out 4–6 months after coronary artery occlusion, well after the time that leukocyte infiltration would have subsided. In addition, Ezra et al demonstrated that tolerance to the vasoconstricting effect of intracoronary leukotriene D4 infusion developed within 2–4 minutes, whereas the decrease in retrograde blood flow in the present study remained stable over the 60-minute observation period. For these reasons, it is unlikely that leukotriene production contributed substantially to indomethacin-induced collateral constriction.
Several investigators have examined the effects of cyclooxygenase blockade in human subjects. In patients with atherosclerotic disease undergoing diagnostic cardiac catheterization, indomethacin has been reported to cause a decrease in coronary sinus blood flow associated with increased myocardial oxygen extraction.36,37 Coronary vasoconstriction in response to cyclooxygenase blockade appears to be facilitated by the presence of coronary artery disease, since Sernesi et al38 failed to find a significant change in coronary hemodynamics in response to cyclooxygenase blockade with ketoprofen (1 mg/kg i.v.) in human subjects with angiographically normal coronary arteries. In these patients, coronary vascular resistance decreased in response to a cold pressor test during control conditions but increased after ketoprofen administration. In a subsequent report, these investigators observed that in patients with coronary artery disease the cold pressor test produced an increase of coronary vascular resistance during control conditions and that this coronary vasoconstriction was exaggerated after ketoprofen administration.39 These findings suggest that vasodilator prostanooids do not influence coronary blood flow during basal conditions in normal human subjects but may exert a vasodilator influence in patients with atherosclerotic coronary artery disease. In addition, prostaglandins appear to inhibit coronary vasoconstriction in both normal subjects and patients with coronary artery disease during the generalized vasoconstrictor response that occurs with the cold pressor test. No data are available examining the effect of cyclooxygenase blockade on blood flow to collateral-dependent myocardium in human subjects.

In summary, cyclooxygenase blockade with indomethacin resulted in substantial decreases of blood flow through moderately well-developed coronary collateral vessels. This occurrence suggests that the endothelial cell hyperplasia previously reported in coronary collateral vessels in this experimental model is associated with increased endothelial production of prostaglandins. The findings of the present study indicate that vasodilator prostaglandins are of importance in optimizing blood flow to the dependent myocardium by maintaining tonic vasodilation of the collateral vessels.

Acknowledgments

The authors wish to acknowledge the expert technical assistance provided by Todd Pavek, Melanie Krampton, Paul Lindstrom, and John Langr. Indomethacin was generously provided by Merck Research Laboratories, West Point, Pa.

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Effect of cyclooxygenase blockade on blood flow through well-developed coronary collateral vessels.
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*Circ Res.* 1992;70:1091-1098
doi: 10.1161/01.RES.70.6.1091

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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