The effect of cyclooxygenase inhibition on vasomotion of proximal coronary arteries with endothelial damage

GARY E. LANE, M.D., AND ALFRED A. BOVE, M.D., PH.D.

ABSTRACT Vasomotion of the proximal branches of the left coronary artery was studied in an intact anesthetized canine preparation after injury to the endothelium of the left anterior descending branch of the left coronary artery (LAD) with a balloon angioplasty catheter. The dimensions of the left coronary artery were examined by quantitative angiography and LAD flow was measured by determining intracoronary $^{133}$Xe washout. Thirty minutes after endothelial damage alone dimensions of the LAD remained unchanged. In five dogs continued observation for a total of 120 min revealed no significant change in dimensions of the LAD. In another group of five dogs, after the administration of 5 mg/kg indomethacin there was a progressive reduction in cross-sectional area of the LAD by 60, 90, and 105 min (37%, 42%, and 50%, respectively, $p < .05$). No significant change in the dimensions of the undamaged left circumflex artery was noted after the administration of indomethacin. The effect of another cyclooxygenase inhibitor (4 mg/kg meclofenamate) on endothelial damage to the LAD in an additional four dogs was also examined. Again significant reduction of the cross-sectional area of the LAD was seen at 60 and 120 min (40% and 44%, respectively, $p < .05$). Heart rate and blood pressure were unchanged throughout the experiment in control and indomethacin-treated dogs. Mean blood pressure rose slightly after administration of meclofenamate (from 80 ± 5 to 98 ± 7 at 120 min, $p < .05$). These data indicate that the combination of endothelial injury and cyclooxygenase inhibition with indomethacin or meclofenamate results in proximal coronary artery vasoconstriction. This phenomenon may have important implications regarding the complications of coronary angioplasty and in focal spasm of diseased coronary arteries.


THE ENDOTHELIUM has been demonstrated in vitro to have an important role in mediating relaxation of vascular smooth muscle. Recently, we used an intact canine preparation to demonstrate an enhanced response to vasoconstrictor agents of proximal coronary arteries with endothelial damage, but factors influencing these phenomena have not been specifically defined. The products of arachidonic acid metabolism may play a role in modulating the vasomotor response, considering the potent effects that such metabolites have been shown to exert on the coronary circulation.

Isolated coronary arteries have been demonstrated to contract in response to disruption of arachidonic acid metabolism by cyclooxygenase inhibition. In addition, balloon catheter-induced damage of canine carotid arteries resulted in a reduction in vasodilator metabolites prostaglandin (PG) I$_2$ and PGE$_2$, while vasoconstrictor metabolites of the lipoxygenase pathway were increased.

The clinical importance of these concepts may be reflected in the complications of balloon coronary angioplasty and the spontaneous vasomotion (spasm) of atherosclerotic coronary arteries. In this study we hypothesized that endothelial damage in the setting of cyclooxygenase blockade would result in significant vasoconstriction of proximal coronary arteries.

Methods

Experimental preparation. Ten adult mongrel dogs were anesthetized with Innovar-vet (0.2 ml/kg im) and ventilated with 70% nitrous oxide in oxygen via a Harvard respirator (model 807). This form of anesthesia produces minimal effects on the coronary circulation.

A No. 6F Lehman catheter and a No. 5F bipolar pacing catheter were advanced under fluoroscopic monitoring through branches of the right external jugular vein into the coronary sinus for blood sampling and pacing. Blood samples for $P_{0_2}$,
oxygen saturation, and hemoglobin were obtained throughout the experimental period.

A coronary guide catheter was advanced under fluoroscopy retrograde through the left carotid artery to the ascending aorta. After engagement of the ostium of the left coronary artery, as determined by test injections of radiopaque contrast medium (meglumine diatrizoate [Renografin-76]), a G20-20 or 20-25S balloon dilatation catheter (USCI) was advanced into the proximal portion of the left anterior descending branch of the left coronary artery (LAD). Statham P23DG pressure transducers were balanced and calibrated for monitoring pressure from the coronary guide catheter, balloon dilatation catheter, and a cannula inserted in the left femoral artery. The pressures and electrocardiogram were monitored continuously and recorded during each stage of the experiment.

Data analysis. Coronary blood flow was determined by injection of 0.25 mCi of $^{133}$Xe through a No. 4F infusion catheter positioned subselectively in the proximal LAD. Radioisotope washout was monitored with a single crystal detector positioned over the left chest at the midventricular level. Count data were processed by a PDP 11/34 computer (Digital Equipment Corp.) and the first 60 sec of the washout curve was used to determine the slope (K) by a monoexponential log-linear least squares calculation. Coronary blood flow was calculated as

$$\text{Flow (ml/min:gm)} = 0.72 \times \text{K/1.05}$$

where 0.72 = myocardium-blood partition coefficient; 1.05 = density of the myocardium.

Coronary vascular resistance (mm Hg/ml/g: min) was calculated from the ratio

$$\text{Mean arterial pressure} \div \text{LAD flow}$$

Dimensions of the left coronary artery were quantitated with a computerized angiographic analysis system. Angiographic examination was performed by injection of 4 to 5 ml of meglumine diatrizoate through the guide catheter into the left main coronary artery. Spot x-ray films were obtained at 85 kV for 35 msec during mid-diastole with an electrocardiographic trigger system. Angiograms were acquired in a constant right anterior oblique projection in each animal. The opacified luminal edges of the coronary artery were manually traced and digitized with a quantitative angiography program in a PDP 11/34 computer (Digital Equipment Corp.). The program calculated luminal diameter and cross-sectional area at 1 mm intervals along the artery measured. A representative 5 mm section of each scanned artery was used to evaluate the results. The method of analysis has been previously tested and described.

Arteriovenous oxygen differences (ml/dl) were calculated by taking the difference between arterial and coronary sinus blood oxygen content. Oxygen content was calculated as (hemoglobin g/100 ml) × 1.35 ml O$_2$/g × oxygen saturation

Experimental procedure. After positioning of the catheters, the baseline heart rate, blood pressure, and coronary blood flow were measured and recorded. Subsequently, an angiogram of the left coronary artery was obtained. After the control measurements, balloon endothelial damage was performed. The balloon dilatation catheter was advanced under fluoroscopic and pressure monitoring to the midportion of the LAD. The balloon was then inflated with a 50% contrast solution under low pressure. While inflated the catheter was withdrawn to the proximal portion of the artery. This procedure was repeated four to five times, during which the fluoroscopic image was recorded on videotape to localize the region of balloon endothelial damage. This method has previously been shown to reliably induce endothelial damage as identified by scanning electron microscopy. Microscopic evaluation of arteries damaged in these experiments revealed findings similar to those of our previous studies. A 2.0 mm balloon was selected for use in arteries with luminal diameters of between 2.0 and 3.0 mm to avoid a myogenic response or possible medial damage.

After endothelial injury, a 30-min period was allowed to eliminate any transient responses. At the end of the 30 min period, the heart rate, pressures, LAD coronary blood flow, and angiographic dimensions were obtained. All animals in the experimental groups sustained endothelial damage as described. In the control group (n = 5), after the stabilization period, serial recording of pressures, heart rate, and coronary dimensions were obtained every 15 min for 90 min. Coronary blood flow measurements were taken at 30 min intervals. In one treated group (n = 5) 5 mg/kg iv indomethacin was administered and pressure, coronary blood flow, and coronary angiographic measurements were recorded as described. In the other treated group (n = 4), 4 mg/kg iv meclofenamate was administered and the same measurements were obtained.

Statistical analysis. Results are reported as mean ± SEM. Data were analyzed with Student’s t test for paired variables and by two-way analysis of variance.

Results

Hemodynamic parameters. The arterial pressure and heart rate did not change significantly throughout the study in the control animals (table 1). The indomethacin-treated animals demonstrated a slight, but nonsignificant, increase in arterial pressure and heart rate after the administration of indomethacin (table 2). In the meclofenamate-treated animals there was a significant increase in arterial pressure from the 30 min measurement until the end of the experiment, and heart rate was unchanged (table 3).

Coronary blood flow and resistance. In the control animals (endothelial damage only) there was a significant decrease in coronary blood flow ($-21%$ at 90 min, p < .05). However, the calculated coronary vascular resistance revealed only a slight, statistically nonsignificant, increase (table 1).

In the indomethacin-treated animals there was a decrease in coronary blood flow and an increase in coronary vascular resistance to values that were not significantly different from initial control values (table 2).

A small but significant rise in coronary blood flow was seen after the endothelial damage procedure was performed in the meclofenamate group ($+34\%$ after endothelial damage, p < .05). The coronary vascular resistance decreased slightly at this point, and increased significantly ($+19\%$, p < .05) at 90 min after the administration of meclofenamate.

Hemoglobin levels were $9.3 \pm 1.6$ g/dl in the control group, $10.6 \pm 1.4$ g/dl in the indomethacin group, and $11.1 \pm 3$ g/dl in the meclofenamate group. There were no significant changes in myocardial arteriovenous oxygen difference throughout the experimental period in either group of animals. Arterial oxygen saturation was 95% to 96% throughout the experiment.
### TABLE 1
Hemodynamic parameters in control animals with endothelial damage only

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>LAD coronary blood flow (ml/min·g)</th>
<th>LAD coronary vascular resistance (mm Hg/ml·g·min)</th>
<th>Myocardial arteriovenous oxygen difference (ml O₂/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>78 ± 7</td>
<td>82 ± 5</td>
<td>1.66 ± 0.09</td>
<td>50 ± 5</td>
<td>5.98 ± 0.70</td>
</tr>
<tr>
<td>15 min</td>
<td>73 ± 7</td>
<td>82 ± 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>77 ± 6</td>
<td>82 ± 4</td>
<td>1.40 ± 0.08</td>
<td>59 ± 4</td>
<td>6.37 ± 0.84</td>
</tr>
<tr>
<td>45 min</td>
<td>74 ± 7</td>
<td>82 ± 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>77 ± 6</td>
<td>80 ± 5</td>
<td>1.66 ± 0.26</td>
<td>57 ± 11</td>
<td>5.84 ± 0.62</td>
</tr>
<tr>
<td>75 min</td>
<td>76 ± 5</td>
<td>84 ± 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>75 ± 7</td>
<td>81 ± 6</td>
<td>1.31 ± 0.08</td>
<td>62 ± 5</td>
<td>6.59 ± 0.80</td>
</tr>
<tr>
<td>105 min</td>
<td>76 ± 7</td>
<td>82 ± 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>77 ± 7</td>
<td>83 ± 7</td>
<td>1.38 ± 0.07</td>
<td>58 ± 4</td>
<td>5.69 ± 0.57</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

*<p < .05 vs control.

### Dimensions of the left coronary artery

Figure 1 illustrates a typical coronary angiogram of the dog left coronary artery after endothelial injury and indomethacin. The midportion of the LAD is narrowed compared with control.

In dogs from the control group (endothelial damage only) the portion of the LAD that sustained endothelial damage did not change significantly in diameter or cross-sectional area for 120 min after the injury (figure 2).

In the dogs in the indomethacin-treated group, there were no significant changes in diameter of cross-sectional area of the undamaged left circumflex coronary artery either before or after drug. In addition, after endothelial damage of the LAD no change in luminal dimensions occurred for 30 min. However, the administration of indomethacin produced a significant reduction in the luminal diameter of the LAD at 60, 90, and 105 min (21%, <p < .02; 25%, <p < .01; and 30%, <p < .01, respectively) vs initial baseline diameter (figure 3). Cross-sectional area was concurrently reduced at 60, 90, and 105 min (37%, <p < .02; 42%, <p < .02; and 50%, <p < .02, respectively) vs initial baseline area (figure 4).

### TABLE 2
Hemodynamic parameters in animals with endothelial damage receiving indomethacin

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>LAD coronary blood flow (ml/min·g)</th>
<th>LAD coronary vascular resistance (mm Hg/ml·g·min)</th>
<th>Myocardial arteriovenous oxygen difference (ml O₂/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>73 ± 8</td>
<td>86 ± 8</td>
<td>2.12 ± 0.59</td>
<td>48 ± 8</td>
<td>6.07 ± 0.28</td>
</tr>
<tr>
<td>Endothelial damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>65 ± 5</td>
<td>85 ± 5</td>
<td>1.81 ± 0.18</td>
<td>49 ± 5</td>
<td>7.15 ± 0.40</td>
</tr>
<tr>
<td>30 min</td>
<td>73 ± 8</td>
<td>85 ± 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>70 ± 5</td>
<td>87 ± 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>70 ± 4</td>
<td>90 ± 5</td>
<td>1.90 ± 0.17</td>
<td>48 ± 5</td>
<td>7.0 ± 0.52</td>
</tr>
<tr>
<td>45 min</td>
<td>70 ± 4</td>
<td>94 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>74 ± 6</td>
<td>89 ± 5</td>
<td>1.63 ± 0.2</td>
<td>55 ± 4</td>
<td>6.99 ± 0.57</td>
</tr>
<tr>
<td>75 min</td>
<td>78 ± 6</td>
<td>94 ± 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>78 ± 7</td>
<td>91 ± 3</td>
<td>1.69 ± 0.24</td>
<td>59 ± 8</td>
<td>7.5 ± 0.60</td>
</tr>
<tr>
<td>105 min</td>
<td>76 ± 6</td>
<td>96 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SEM.
TABLE 3
Hemodynamic parameters in animals with endothelial damage receiving meclofenamate

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>LAD coronary blood flow (ml/min·g)</th>
<th>LAD coronary vascular resistance (mm Hg/ml·g·min)</th>
<th>Myocardial arteriovenous oxygen difference (ml O2/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>72 ± 15</td>
<td>80 ± 5</td>
<td>2.03 ± 0.43</td>
<td>48 ± 14</td>
<td>6.76 ± 0.49</td>
</tr>
<tr>
<td>Endothelial damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>80 ± 14</td>
<td>91 ± 6</td>
<td>2.73 ± 0.47&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 ± 5</td>
<td>6.86 ± 0.64</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>72 ± 13</td>
<td>94 ± 3</td>
<td>2.09 ± 0.56</td>
<td>51 ± 11</td>
<td>7.35 ± 0.26</td>
</tr>
<tr>
<td>30 min</td>
<td>71 ± 10</td>
<td>92 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.07 ± 0.46</td>
<td>51 ± 11</td>
<td>7.12 ± 0.33</td>
</tr>
<tr>
<td>60 min</td>
<td>71 ± 8</td>
<td>94 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.27 ± 0.47</td>
<td>47 ± 9</td>
<td>7.44 ± 0.69</td>
</tr>
<tr>
<td>90 min</td>
<td>74 ± 11</td>
<td>96 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.04 ± 0.50</td>
<td>57 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.14 ± 0.30</td>
</tr>
<tr>
<td>120 min</td>
<td>71 ± 10</td>
<td>98 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.18 ± 0.49</td>
<td>55 ± 17</td>
<td>7.90 ± 0.51&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>NTG</td>
<td>72 ± 9</td>
<td>96 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>7.76 ± 0.39</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. NTG = nitroglycerin.<sup>a</sup>p < .05.

Analysis of the dimensions of the LAD in the group treated with meclofenamate (n = 4) also revealed a significant reduction in diameter at 60, 90, and 120 min (21%, 18%, and 27%, respectively, all p < .05). Cross-sectional area (figure 5) was concurrently reduced at 60 and 120 min (40% and 49%, respectively, p < .05). After the administration of 200 µg of intracoronary nitroglycerin the dimensions of the LAD returned to baseline in both the indomethacin and meclofenamate groups.

Discussion
We have demonstrated significant vasoconstriction of endothelial-damaged proximal LADs in the setting of cyclooxygenase inhibition. Indomethacin did not affect the dimensions of the undamaged left circumflex coronary artery, and control animals with endothelial damage alone did not have significant constriction. Significant vasoconstriction of damaged LADs was also seen in a group of meclofenamate-treated dogs. The similar effect of indomethacin and meclofenamate

FIGURE 1. Right anterior oblique left coronary angiogram from an intact dog before (top) and after combined indomethacin and endothelial injury (bottom). There is a focally narrowed area in the mid portion of the LAD (arrow).

FIGURE 2. Diameter of mid portion of LAD measured by quantitative coronary angiography over a 120 min period after endothelial damage (ED). Data expressed as mean ± SEM.
The reduction in the dimensions of the damaged coronary arteries in the group treated with indomethacin or meclofenamate could not be explained by a decrease in myocardial metabolic demands, since the heart rate and blood pressure actually increased slightly during the experiment.

There was also no significant alteration of coronary blood flow or coronary vascular resistance in the group treated with indomethacin. A small but significant increase in coronary vascular resistance was noted 90 min after the administration of meclofenamate. These measurements were made in dogs in the resting state and no attempt was made to determine the coronary flow reserve during the vasoconstriction. It is probable that the degree of vasoconstriction seen in this experiment would result in a serious limitation to nutrient flow through a coronary arterial lumen previously compromised to a moderate degree by an atherosclerotic stenosis.

Intravenous indomethacin has been shown to slightly decrease resting coronary blood flow and in some experiments to diminish the reactive hyperemic response in open-chest or isolated heart canine preparations. However, in other anesthetized animal preparations a significant alteration of resting coronary blood flow or coronary vascular resistance has not been observed. Indomethacin causes contraction of isolated coronary artery strips in vitro. In addition, isolated balloon-dilated canine carotid arterial segments exhibit an enhanced contractile response to nor epinephrine after the addition of indomethacin. The

FIGURE 3. Diameter of mid portion of LAD and circumflex (LCX) coronary arteries measured by quantitative angiography over 105 min after endothelial damage (ED) to the LAD and intravenous indomethacin (IND). The LAD showed a progressive focal narrowing in the endothelial-damaged segment. NTG = nitroglycerin. Data expressed as mean ± SEM.

FIGURE 4. Cross-sectional area of LAD and circumflex (LCX) coronary arteries after endothelial damage (ED) to the LAD and indomethacin (IND). NTG = nitroglycerin. Data expressed as mean ± SEM.

FIGURE 5. Cross-sectional area of the LAD after endothelial damage (ED) and meclofenamate (MEC). NTG = nitroglycerin. Data are expressed as mean ± SEM.
principal action of indomethacin is to inhibit the enzyme cyclooxygenase.\textsuperscript{20} Another cyclooxygenase inhibitor, acetylsalicylic acid, has also been shown to contract isolated coronary arterial preparations.\textsuperscript{5,7} In man, Freidman et al.\textsuperscript{21} have demonstrated a substantial fall in coronary blood flow (181 to 111 ml/min) and a rise in coronary vascular resistance (+73%) in response to the administration of intravenous indomethacin (0.5 mg/kg) to patients with coronary artery disease. The exact mechanism underlying this response has not been elucidated. In particular, it is unknown whether this elevation of coronary resistance occurs because of vasoconstriction within the distal resistance vasculature or at the level of proximal conductance in coronary arteries with significant stenoses.

Recently, extensive investigation in vitro has documented the importance of the endothelium in the regulation of vasomotion.\textsuperscript{1} The responses (especially relaxation) of vascular smooth muscle to many neurohumoral mediators are endothelium-dependent. The endothelium is susceptible to many toxic or mechanical injury processes. For example, coronary transluminal balloon angioplasty causes a loss of endothelium and platelet adhesion to the denuded arterial wall.\textsuperscript{22} Also, endothelial damage has been postulated to be an important feature in the evolution of an atherosclerotic stenosis.\textsuperscript{23} These examples illustrate how endothelial-damaged vessels may potentiate abnormal vasoconstrictor responses of proximal coronary arteries.

Derivatives of arachidonic acid have been demonstrated to produce impressive effects on the coronary circulation. Prostacyclin plays an important role in controlling platelet aggregation on vascular endothelium.\textsuperscript{24} In addition, it is a potent coronary vasodilator.\textsuperscript{25} Infusion of thromboxane A\textsubscript{2} into coronary arteries will result in vasoconstriction.\textsuperscript{26} Recently, products of the alternative pathway of arachidonic acid metabolism (via lipoxygenase) have also been demonstrated to exert impressive effects on the coronary circulation.\textsuperscript{27,28} Leukotrienes C\textsubscript{4}, D\textsubscript{4}, and E\textsubscript{4} (originally described as slow-reacting substance of anaphylaxis or SRS-A) have been shown to provoke potent coronary vasoconstriction resulting in significant ischemia in several animal preparations.\textsuperscript{29-32}

Trauma induced by the angioplasty balloon catheter does result in an alteration of arachidonic acid metabolism, which in turn results in a decrease in vasodilator PGs such as prostacyclin and an increase in lipoxygenase products.\textsuperscript{8} Coronary arteries that sustained endothelial damage alone in our experiments did not manifest vasoconstriction. Intervention into the metabolic pathway of arachidonic acid by inhibition of the enzyme cyclooxygenase with indomethacin did result in significant vasoconstriction. Experimental evidence has demonstrated enhanced release of anaphylactic mediators (SRS\textsuperscript{2}A) from lung, enhancement of antigen-induced tracheal contraction,\textsuperscript{33} and increased production of chemotactic factors in the presence of cyclooxygenase inhibitors.\textsuperscript{34} These findings suggest that inhibition of cyclooxygenase may result in preferential metabolism of arachidonic acid via the lipoxygenase pathway with the production of vasoconstrictor leukotrienes.\textsuperscript{35} This shift in metabolism may accentuate the production of lipoxygenase products as previously described in balloon catheter–traumatized canine carotid arteries.\textsuperscript{8} Alternatively, a reduction in the amount of prostacyclin present in the arterial wall caused by a combination of trauma and cyclooxygenase inhibition could result in vasoconstriction. The precise alteration in arachidonic acid metabolism responsible for the results cannot be specified with the available data.

A direct vasoconstrictor action of indomethacin on endothelial-damaged arteries could be postulated. However, the temporal course of the vasoconstrictor would suggest an action requiring time for alteration of a biosynthetic pathway. Further experimentation should allow for a more accurate explanation of the vasoconstrictor response. Kalsner\textsuperscript{7} has demonstrated contraction of coronary artery preparations in vitro by aspirin and indomethacin. Addition of one inhibitor followed by the other did not potentiate the vasoconstriction, suggesting a similar mechanism of action for the two agents in these experiments in vitro. In addition, vasoconstriction induced by meclofenamate in the present study would also support the importance of cyclooxygenase inhibition in mediating the vasoconstrictor response.

**Methodologic considerations.** The procedure of balloon catheter–induced endothelial injury used in these experiments has been previously shown to reliably result in extensive endothelial loss with platelet aggregation.\textsuperscript{2} The technique described was used after consideration of several factors, including the significance of endothelial damage in modulating vasomotor responses. The importance of avoiding a myogenic response, and possibly overdistending the artery resulting in paralysis of the muscular media was considered.\textsuperscript{36} Although possibly not completely analogous to clinical coronary angioplasty, this preparation does reproduce the common occurrence of endothelial injury. In addition, it is unlikely that extensive medial damage occurs often during clinical coronary angioplasty, in view of the relatively common occurrence of spasm in this setting.\textsuperscript{37}
Isolated artery preparations have been described to undergo indomethacin-induced vasoconstriction even when no procedures are performed to induce endothelial injury. It is possible that inadvertent endothelial injury occurred in these preparations or that the dose of indomethacin responsible for the effects seen was not analogous to the dose used in our experiments. Use of acetylcholine as a spasmogen in some of these experiments would support the former possibility. Also, interaction between blood and the vessel wall is not allowed for in the experiments in vitro.

The doses of indomethacin and meclofenamate used in our experiments were selected because they have been shown to be effective in inducing cyclooxygenase inhibition in the canine coronary circulation. It should also be noted that neither indomethacin or meclofenamate prevented a proximal coronary artery vasodilator response to intracoronary nitroglycerin.

**Clinical importance of findings.** Percutaneous transluminal coronary angioplasty results in extensive endothelial damage. Coronary artery spasm occurs in 4% to 5% of the coronary angioplasty procedures. One third of these episodes of spasm are associated with major complications such as myocardial infarction, emergency coronary artery bypass surgery, or death. There are data to suggest that coronary artery spasm plays a major role in the development of acute occlusion after percutaneous coronary angioplasty. Many patients undergoing this procedure receive cyclooxygenase inhibitors for their antiplatelet effects. Our work suggests that the interaction of endothelial injury and cyclooxygenase inhibition may lead to a propensity for vasoconstriction of the proximal coronary artery. However, the dose of cyclooxygenase inhibitor used in our study was equivalent to doses used for treatment of inflammatory disorders and platelet-inhibitory doses are generally lower.

As mentioned previously, the study of Friedman et al. demonstrated a substantial elevation of coronary vascular resistance by indomethacin in patients with atherosclerotic coronary artery disease. The anatomic site of this vasoconstrictor effect has not been localized. It is possible that the diseased proximal coronary arteries of these patients provided a setting for the vasoconstrictor action of indomethacin at the site of atherosclerotic stenoses. This could explain the decrease in coronary blood flow noted in these patients.

In conclusion, we have demonstrated an important interaction of endothelial injury of normal coronary arteries and cyclooxygenase inhibition that resulted in a coronary vasoconstrictor response in an intact anesthetized canine preparation. Further study of this phenomenon should allow for greater understanding of the role of PGs and leukotrienes in the pathogenesis of abnormal coronary vasomotion.

We thank Messers. J. Dewey, C. Grabau, and R. Owen for technical assistance and Mrs. L. Schwieder for preparing the manuscript.

**References**

22. Pasternak RC, Baughman KL, Fallout JT, Block PC: Scanning
The effect of cyclooxygenase inhibition on vasomotion of proximal coronary arteries with endothelial damage.
G E Lane and A A Bove

_Circulation_. 1985;72:389-396
doi: 10.1161/01.CIR.72.2.389
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/72/2/389

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/