Dissimilar Effects of Prostacyclin, Prostaglandin E₁, and Prostaglandin E₂ on Myocardial Infarct Size after Coronary Occlusion in Conscious Dogs

Bodh I. Jugdutt, Grover M. Hutchins, Bernadine H. Bulkley, and Lewis C. Becker

SUMMARY We studied the effects of prostaglandin E₁ (PGE₁), PGE₂, and prostacyclin (PGI₂) on collateral blood flow (CBF) and myocardial infarct size in conscious dogs. Beginning 5 minutes after acute permanent occlusion of the mid left circumflex coronary artery, 6-hour infusions of PGE₁ (0.6 μg/kg per min in 150 ml saline, 13 dogs), PGE₂ (0.7 μg/kg per min in 150 ml saline, 11 dogs), PGI₂ (0.5 μg/kg per min in 150 ml saline, 19 dogs) or saline alone (150 ml, 15 control dogs) were given into the left atrium. In the three treatment groups, similar reductions occurred in mean arterial pressure (PGE₁, 11%; PGE₂, 10%; PGI₂, 5%) and mean left atrial pressure (PGE₁, 44%; PGE₂, 30%; PGI₂, 36%), whereas heart rate was unchanged. Mean arterial pressure remained above 80 mm Hg throughout the infusions. After the dogs were killed 2 days later, the boundaries of the occluded bed were defined by coronary arteriography. The mass of infarct and occluded bed were measured by planimetry of weighed transverse sections of the left ventricle (LV). Although the mass of occluded bed and LV were similar in the four groups, infarct size was significantly less (<0.005) with PGI₂ and PGE₁ compared to PGE₂ or controls, both as percent LV (4.7 vs. 7.3 vs. 14.4 vs. 14.8%, respectively) and as percent of the occluded bed (12.3 vs. 16.4 vs. 38.5 vs. 37.7%, respectively). Over the 6-hour infusion period, CBF (7-10 μm radioactive microspheres) increased throughout the occluded bed in PGI₂ and PGE₁ but not in PGE₁ and control dogs. Transmural CBF (ml/min per g) by the 8th hour, in the center of the infarct region, was greater (P < 0.05) in PGI₂ (0.30 ± 0.05) and PGE₁ (0.28 ± 0.04) than in PGE₂ (0.09 ± 0.03) or control dogs (0.11 ± 0.01). Since peripheral hemodynamic effects with the different PG's were similar, myocardial protection with PGI₂ and PGE₁ appears to be attributable largely to the increase in collateral flow. However, both PGI₂ and PGE₁ also produced myocardial salvage in hearts with low levels of collateral flow, suggesting that cellular and metabolic effects may also have contributed to their protective action.


AFTER coronary artery occlusion, survival of acutely ischemic myocardium depends on collateral blood supply, myocardial oxygen demands, and metabolic and cellular conditions and other processes (Maroko and Braunwald, 1976). Since prostaglandins (PG's) have vasoactive properties (Nakanoto et al., 1967; Bloor et al., 1973; Rowe et al., 1974) and exert metabolic and cellular effects (Malik and McGiff, 1977; Needelman and Kaley, 1978), they might be expected to have an important influence on the course of ischemic myocardial necrosis. This notion is supported by findings from several experiments. First, early release of endogenous PG's occurs during myocardial ischemia (Berger et al., 1976; Ogletree et al., 1977). Second, the potent inhibitor of PG synthesis, indomethacin, (1) inhibits PG release during myocardial ischemia (Ogletree et al., 1977), (2) increases the extent of myocardial ischemic injury and decreases collateral blood flow in anesthetized dogs (Kirmser et al., 1976), and (3) increases myocardial infarct size in conscious dogs (Jugdutt et al., 1979a).

The PG's in the E series cause systemic and coronary arterial dilation in nearly all species (Nutier et al., 1972; Strong et al., 1976; Needelman et al., 1978), and might therefore be expected to lessen ischemic injury by reducing myocardial oxygen demands and increasing collateral blood flow. Prostacyclin (PGI₂), which is the major active metabolite of arachidonic acid in vascular endothelium (Moncada et al., 1976, 1977; Dusting et al., 1977; Raz et al., 1977; Needelman and Kaley, 1978), and produces both potent inhibition of platelet aggregation (Moncada et al., 1976, 1977) and potent vasodilation (Dusting et al., 1977), especially of coronary arteries (Dusting et al., 1977; Raz et al.,
In this study, we examined the effects of PGE$_1$, PGE$_2$, and PGF$_1$ on collateral blood flow and ultimate pathological infarct size after coronary artery occlusion in conscious dogs. We administered the PG's in pharmacological doses needed to produce similar mild reductions in arterial pressure. In an attempt to optimize the effect of therapy on ischemic myocardium, we gave the PG's over the first 6 hours post-occlusion, beginning as early as possible after the onset of ischemia (5 minutes postocclusion). A conscious dog model was used, in which infarct size is measured relative to the size of the occluded bed (Jugdutt et al., 1979b). In previous studies, we have found this approach to be a sensitive method for determining the effect of interventions on infarct size (Jugdutt et al., 1979a, 1980, 1981).

**Methods**

Under general anaesthesia (sodium pentobarbita-
tal, 25-35 mg/kg, iv) and through a left lateral thoracotomy, 76 mongrel dogs weighing 18-23 kg each had a plastic occluder snare placed around the left circumflex (LC) coronary artery just distal to the first large marginal branch and plastic catheters inserted into an external jugular vein, common carotid artery, and the left atrial appendage. The distal ends of the catheters and snare were tun-
nelled subcutaneously and the catheters were filled with heparinized saline and exteriorized at the back of the neck. After surgery, penicillin (1 million units) and streptomycin (1 g) were given intramuscularly.

Experiments were done on 71 healthy surviving dogs 7-10 days later. While they stood in a sling opposite points through the walls of the left ventri-
elve level (Lowe et al., 1978). The injected hearts were packed with gauze to maintain diastolic pressure within 2-5 g). The viscosity of the injection mass was such that no penetration occurred beyond the precapil-
ary level (Lowe et al., 1978). The injected hearts were then killed after a lethal dose of anesthetic, the heart removed, washed free of blood, and weighed.

**Measurement of Occluded Bed Size and Infarct Size**

Postmortem stereoscopic coronary arteriography (Fulton, 1965; Schaper, 1971; Jugdutt et al., 1979a, 1979b) was performed on all fresh hearts to visualize vessels in both occluded and unoccluded coronary beds. Simultaneous injections of a barium sulphate-
gelatin mass were made under a controlled pressure of 160 mm Hg via canulas placed at the origins of the right, left anterior descending (LAD), and LC coronary arteries. The mean weight gain from the injections (volume of about 5 ml) was 3.5 g (range 2-5 g). The viscosity of the injection mass was such that no penetration occurred beyond the precapil-
ary level (Lowe et al., 1978). The injected hearts were packed with gauze to maintain diastolic pro-
portions, before being fixed in 20% formalin, and radiographed stereoscopically. Completeness of the occlusion was confirmed by finding an abrupt inter-
ruption in the arteriogram of the LC artery with non-filling of a short segment. In all hearts, arteriograms visualized the unoccluded bed as well as the occluded LC bed which filled via collateral channels from non-occluded vessels. The hearts were cut into five transverse sections (1-1.5 cm thick), from the level of the occlusion at the base to the apex. To facilitate orientation of the radiographs and LV sections, metallic wire markers were placed at two opposite points through the walls of the left ventri-
cle (LV) in each transverse section, and paired

**Postocclusion Hemodynamic Recordings**

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cle (LV) in each transverse section, and paired
stereoscopic radiographs were made. Major coronary artery branches were identified in the whole heart radiographs as originating from unoccluded vessels or from the LC artery distal to the occlusion. The epicardial and transmural course of each branch was then determined using the whole heart radiographs repeatedly as a reference. The anatomic boundaries between occluded and unoccluded vascular beds were then marked by a consensus of two observers on the coded radiographs of the transverse sections, without knowledge of treatment given. These tracings were then transferred to tracings of LV rings and infarcts in each heart by making sets of 22 measurements with fine calipers at 14 chosen points in each ring (Fig. 1). Only dogs with visible infarcts were included in this latter analysis.

The LV transverse sections from each heart were weighed after removal of the right ventricle, fatty, and valvular tissue, and large epicardial vessels. Outlines of each LV ring and the infarct (identified by gross inspection of the unstained, formalin-fixed ring), were traced on a transparent plastic overlay without knowledge of treatment given. These tracings were then superimposed on the marked radiographs of the transverse sections and aligned using the radioopaque metallic markers, as well as natural anatomic markers such as the cavity contour, the papillary muscles, the septum, and junctions with the right ventricle. The markings of occluded bed boundaries were copied and transferred to the LV rings to facilitate tissue sampling for RMBF measurements. Areas of the LV rings, occluded beds, and infarcts were planimetered electronically. Masses of the infarcts and occluded beds for each ring were computed by relating their average areas (from top and bottom surfaces on each LV ring) to the weights of the rings (Jugdutt et al., 1979b).

Areas of infarct outlines made by two independent observers in 12 hearts differed by an average of 2% (± 580 observations), indicating good interobserver reproducibility. Total masses of infarct and occluded beds were calculated for each heart by summing the values for the individual rings. Maps were plotted to show the relationship of the infarct within the occluded bed for each LV ring from base to apex in the four treatment groups by making sets of 22 measurements with fine calipers at 14 chosen points in each ring (Fig. 1). Only dogs with visible infarcts were included in this latter analysis.

**Figure 1** Schematic of the method used to spatially reconstruct maps of the infarct within the occluded region, from base to apex of the left ventricle (LV), for the four groups. Boundaries of the occluded bed were first marked on arteriograms of LV transverse sections and then transferred to tracings of LV rings and infarcts superimposed on the radiographs. In each LV ring tracing, measurements were made (in mm) within the occluded region along lines numbered 1–13. At lateral borders of the occluded bed, thicknesses were measured along 4, 5, 9, and 10, and measurements 1 and 11, 3 and 13 were averaged. Within the infarct, measurements were made at equal intervals, and corresponding values from endocardial (2a to 2d) and epicardial (12a to 12d) surfaces were averaged. The thickness of the infarct (6b, 7b, 8b) and the uninfarcted outer rim (6a, 7a, 8a) was measured.
Measurements of Regional Myocardial Blood Flow (RMBF)

For measurements of RMBF, transmural samples (0.5–3 g) were taken serially throughout the occluded bed from each LV ring so as to include the center of the infarct, the adjacent margins of the infarct (5 mm within the infarct boundary on the endocardial surface), the visually normal border tissue, located between the occluded bed boundaries and the endocardial edge of the infarct (Fig. 1). In addition, transmural samples (2–3 g) were taken from the center of the non-ischemic LAD coronary artery bed near the anterior papillary muscle. The upper surfaces of samples within the occluded bed from the mid LV ring of each heart were marked with bromochrome for histology. All transmural samples were divided into inner and outer halves, which were weighed, placed in vials containing 10% formalin, and counted for radioactivity together with the reference blood samples in a well-type γ scintillation counter (Packard #5986) at five energy windows adjusted to the peak emission of the five nuclides. RMBF (ml/min per g) was calculated from the formula: RMBF = Cm × RBF/Cr, where Cm = corrected counts/g in myocardial samples, RBF = reference blood flow (withdrawal rate of the Harvard pump), Cr = counts in the reference blood sample. We calculated flows in four main regions (the center and margins of the infarct, the visually normal borders of the infarct in the occluded LC bed, and the non-ischemic LAD regions) for each dog by pooling samples in corresponding regions. Coronary vascular resistance in each region was calculated by dividing mean flow by mean arterial pressure.

Histology

Planimeted visual necrosis was correlated with histological necrosis. Formalin-fixed tissue samples from infarcted regions of the middle LV ring of each heart were embedded in paraffin and histological sections made in the same planes as the planimeted surfaces (identified by bromochrome). The sections were coded, stained with hematoxylin and eosin, and examined independently for the distribution and amount of necrosis by two of us (GH, BJ). The estimates of total necrosis per sample (to the nearest 5%) made by the two observers were in close agreement (y = 0.97 x + 4.8, r = 0.96, n = 120) and differed by an average of 5 ± 0.5%. The percent visual necrosis and percent histological necrosis were in close agreement (visual = 0.96 histologic + 6.82, r = 0.94, n = 120, P < 0.001).

Statistics

The statistical methods used were as follows: (1) analyses of variance (ANOVA), to calculate the significance of differences within and between groups; (2) linear regression analysis by the least square fit method, and the significance of r values and slopes by ANOVA; (3) the 2 by 4 χ2 test (with ANOVA and Duncan’s tests) to assess the significance of differences in event frequency between groups; (4) repeated measures ANOVA with orthogonal contrast for analyzing changes in sequential post-occlusion flows in different regions within groups, and trend analysis for comparing changes between groups. Separate analyses, using multiple comparisons least significant difference test (LSD) based on ANOVA, were done for flow in endocardial and epicardial layers and transmural flows within each region. Results are given as mean ± standard error of the mean, and P values.

Results

Mortality and Morbidity

Of the 71 dogs that were studied, all survived the first 5 minutes of LC occlusion, but 13 developed ventricular fibrillation over the next 5 hours and died: seven from the saline group (at 15, 20, 30, 40, 60, 120, and 300 minutes post-occlusion), two from the PGI1 group (at 15 and 20 minutes post-occlusion), one from the PGE1 group (at 15 minutes post-occlusion), and three from the PGE2 group (15, 20, and 35 minutes post-occlusion). No statistically significant differences in mortality were found among the four groups (control: 7 of 22; PGI1: 2 of 21; PGE1: 1 of 14; PGE2: 3 of 14; χ2 = 5.03, P = 0.168). The size of the occluded beds among these early deaths were within the range of values for the four groups. In the PGE2 group, nine of the 14 dogs developed at least one episode of vomiting and diarrhea within a few minutes of starting the infusion, but no obvious side effects were detected in dogs receiving PGE1 or PGI1. The data on the 58 dogs that survived 2 days form the basis of this report: 15 saline controls, 19 PGI1-treated, 13 PGE1-treated and 11 PGE2-treated.

Hemodynamics

Hemodynamic changes in the four treatment groups are summarized in Table 1. Pre-occlusion heart rate, mean arterial pressure, and mean left atrial pressure were similar. After coronary occlusion, heart rate and left atrial pressure increased significantly (P < 0.001), but mean arterial pressure did not change. These changes were maintained over the next 6 hours in the saline group. Mean arterial pressure was reduced similarly by PGI1 (122 to 116 mm Hg, P < 0.001, 5% reduction), PGE1 (115 to 102 mm Hg, P < 0.001, 11% reduction) and PGE2 (119 to 107 mm Hg, P < 0.001, 10% reduction) and the decreases were sustained over the 6-hour infusion period. Mean left atrial pressure was also reduced similarly by PGI1 (11 to 7 mm Hg, P < 0.001), PGE1 (9 to 5 mm Hg, P < 0.001) and PGE2 (10 to 7 mm Hg, P < 0.001) and the decreases were again sustained over the 6-hour infusion period. However,
heart rate did not change during the PGI2, PGE1, and PGE2 infusions, and did not differ significantly from that in the control group. Throughout the PGI2, PGE1, and PGE2 infusions, mean arterial pressure remained above 80 mm Hg.

**Electrocardiograms**

In all dogs, post-occlusion ECG’s showed ST-segment elevation in limb leads 2, 3, aVr. Periods of premature ventricular activity (≥3 minutes of ectopic activity, 3 minutes apart) were more frequent in the group treated with saline than the group treated with PGI2 (6.9 ± 1.1 vs. 1.1 ± 0.3, P < 0.001) or PGE1 (6.9 ± 1.1 vs. 1.6 ± 0.3, P < 0.001) or PGE2 (6.9 ± 1.1 vs. 1.2 ± 0.4, P < 0.001), but there was no significant difference in their frequency in PGI2, PGE1, and PGE2 groups (1.1 vs. 1.6 vs. 1.2). At 2 days, significant Q waves (greater than 0.03 second and 0.2 mV) in leads 2, 3, aVr, were found in more saline (9 of 15) and PGE2 (7 of 11) treated dogs than in the PGI2 (1 of 19) and PGE1 (4 of 13) treated dogs, but the differences were not statistically significant except when comparing PGI2 and saline-treated dogs (χ² = 12.10, P < 0.005). The average Lown score of ventricular arrhythmias 2 days post-occlusion in saline-treated dogs (1.67 ± 0.40) was significantly higher than in PGI2-treated dogs (0.33 ± 0.24, P < 0.01) but was not different from that in the PGE1 (1.1 ± 0.4, NS) and PGE2 (0.8 ± 0.3, NS) treated dogs.

**Infarct Size**

Both PGI2 and PGE1 treatment significantly reduced total infarct size, measured in grams, as percent of left ventricle, and as percent of the occluded bed, compared to treatment with PGE2 or saline. Infarct size was not significantly different between PGE2 and saline groups (Fig. 2; Table 2). As noted previously, a wide range of infarct size and occluded bed size was found despite occlusions being made at a constant anatomic site (Jugdutt et al., 1979a, 1979ab, 1980, 1981; Lowe et al., 1978).

In each of the four groups, infarct size, as percent LV, was closely related to the size of the occluded bed, as percent LV (Fig. 3). The slope of the linear regression was significantly less (P < 0.005) with PGE1 (0.54) and PGI2 (0.46) compared to saline (1.03) or PGE2 (1.15). The horizontal axis intercept, obtained by extrapolation, was 20.9% of the LV for the saline group, suggesting that no infarcts developed for occluded beds below this size. The horizontal axis intercept for PGE2 was similar to that for controls (21.2 vs. 20.9% LV, NS). In contrast, the horizontal axis intercept for PGE1 (26.3% LV) was significantly (P < 0.05) displaced to the right compared to those for control and PGE2 groups, suggesting that larger occluded beds are required before infarction is seen after PGE1. With PGI2 the horizontal axis intercept was 24.3% LV, indicating a slight shift to the right (NS). However, inspection of Figure 3 reveals that five PGI2-treated dogs with

### Table 1: Hemodynamics in Saline-, Prostacyclin (PGI2), PGE1-, and PGE2-Treated Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Timing</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Mean left atrial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 15)</td>
<td>Pre-occlusion</td>
<td>103 ± 4</td>
<td>122 ± 3</td>
<td>7 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>129 ± 4*</td>
<td>122 ± 5</td>
<td>11 ± 0.7*</td>
</tr>
<tr>
<td></td>
<td>20 sec</td>
<td>122 ± 3</td>
<td>124 ± 3</td>
<td>11 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>118 ± 2</td>
<td>119 ± 4</td>
<td>10 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>1 hour</td>
<td>117 ± 3</td>
<td>119 ± 3</td>
<td>10 ± 0.6</td>
</tr>
<tr>
<td>PGI2 (n = 19)</td>
<td>Pre-occlusion</td>
<td>106 ± 4</td>
<td>121 ± 3</td>
<td>7 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>126 ± 5*</td>
<td>122 ± 3</td>
<td>11 ± 0.7*</td>
</tr>
<tr>
<td></td>
<td>20 sec</td>
<td>119 ± 4†</td>
<td>118 ± 3†</td>
<td>7 ± 0.6†</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>117 ± 5</td>
<td>117 ± 3</td>
<td>8 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>1 hour</td>
<td>120 ± 3</td>
<td>116 ± 3</td>
<td>8 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>101 ± 6</td>
<td>121 ± 4</td>
<td>6 ± 0.5</td>
</tr>
<tr>
<td>PGE1 (n = 11)</td>
<td>Pre-occlusion</td>
<td>120 ± 6</td>
<td>119 ± 4</td>
<td>10 ± 0.7*</td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>124 ± 6</td>
<td>106 ± 5†</td>
<td>8 ± 1.0†</td>
</tr>
<tr>
<td></td>
<td>20 sec</td>
<td>126 ± 4</td>
<td>102 ± 3</td>
<td>6 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>127 ± 4</td>
<td>98 ± 3</td>
<td>7 ± 0.7</td>
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<tr>
<td></td>
<td>1 hour</td>
<td>120 ± 5</td>
<td>101 ± 3</td>
<td>5 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>121 ± 7</td>
<td>98 ± 2</td>
<td>6 ± 1.0</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM.

*P < 0.001, significance of 20 sec post-occlusion vs. pre-occlusion value.

†P < 0.05, significance of value immediately after PGI2, PGE1, or PGE2 compared to 20 sec value.
occluded beds between 30 and 36% of LV mass had small (<2% LV) or no infarcts, suggesting that larger occluded beds are in fact required before infarction is seen after PGI₂. Significant rightward displacement of the extrapolated horizontal axis intercept for the PGI₂ group relative to that for controls was found (29 vs. 18%, P < 0.01) when linear regressions were replotted after arbitrarily excluding hearts with occluded beds less than 30% LV from both groups.

PGI₂ and PGE₁, but not PGE₂, altered the geometric relationship of infarct to occluded bed (Fig. 4). In all four groups, the infarct and occluded bed were larger in basal and middle portions of the LV and tapered toward the apex. The infarct:occluded bed ratio was greater in basal than in apical rings in the saline-treated (47 ± 5% vs. 26 ± 8%, P < 0.01), PGI₂ (19 ± 4% vs. 8 ± 3%, P < 0.01), PGE₁-treated (21 ± 4% vs. 16 ± 5%, NS), and PGE₂-treated (46 ± 7% vs. 32 ± 4%, NS) groups. With both PGE₁ and PGI₂, the absolute mass of the infarct and the infarct:occluded bed ratio in all LV rings were less (P < 0.05) compared to PGE₂ and saline controls, but this effect was more marked with PGI₂. Thus,

![Figure 2](image)

**Figure 2** PGE₁ (E₁) and PGI₂ (E₂) reduced infarct size compared to controls (C) and PGE₂ (E₂ both in grams, on the left, and as percent left ventricle or percent of the occluded bed, on the right. The mass of the occluded bed and left ventricle were not significantly different among the four groups (*P < 0.05, **P < 0.005, ***P < 0.001 vs. C or E₂ groups). Means ± SEM for the groups are shown.

### Table 2

**Effect of PGE₁, PGE₂, and PGI₂ on Myocardial Infarct Size in Conscious Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Infarct mass (g)</th>
<th>Occluded bed mass (g)</th>
<th>LV mass (g)</th>
<th>Infarct/LV (%)</th>
<th>Occluded bed/LV (%)</th>
<th>Infarct/occluded bed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(n = 15)</td>
<td>13.7 ± 2.7</td>
<td>32.6 ± 2.7</td>
<td>92.2 ± 2.9</td>
<td>14.8 ± 2.9</td>
<td>35.4 ± 2.8</td>
<td>37.7 ± 5.4</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(10–39.2)</td>
<td>(20.4–60.2)</td>
<td>(76.0–118.7)</td>
<td>(0–41.4)</td>
<td>(21.6–63.4)</td>
<td>(0–67.5)</td>
</tr>
<tr>
<td><strong>PGE₁</strong></td>
<td>12.8 ± 3.0</td>
<td>28.9 ± 2.8</td>
<td>85.2 ± 3.7</td>
<td>14.4 ± 3.6</td>
<td>33.7 ± 2.4</td>
<td>38.5 ± 6.8</td>
</tr>
<tr>
<td>(n = 11)</td>
<td>(0–37.4)</td>
<td>(16.2–51.4)</td>
<td>(70.4–111.1)</td>
<td>(0–33.8)</td>
<td>(20.4–46.3)</td>
<td>(0–72.8)</td>
</tr>
<tr>
<td><strong>PGE₂</strong></td>
<td>6.4 ± 1.4*</td>
<td>34.2 ± 2.6</td>
<td>85.6 ± 2.9</td>
<td>7.3 ± 1.5*</td>
<td>30.6 ± 2.5</td>
<td>16.4 ± 2.9†</td>
</tr>
<tr>
<td>(n = 13)</td>
<td>(0–17.6)</td>
<td>(18.0–52.9)</td>
<td>(65.0–100.1)</td>
<td>(0–17.6)</td>
<td>(23.7–52.8)</td>
<td>(0–33.2)</td>
</tr>
<tr>
<td><strong>PGI₂</strong></td>
<td>4.7 ± 1.0†</td>
<td>33.2 ± 2.2</td>
<td>96.3 ± 3.9</td>
<td>4.7 ± 1.0†</td>
<td>34.4 ± 1.6</td>
<td>12.3 ± 2.1†</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(0–14.3)</td>
<td>(19.2–55.9)</td>
<td>(63.1–126.7)</td>
<td>(0–12.4)</td>
<td>(18.5–48.3)</td>
<td>(0–30.1)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. Abbreviations: LV = left ventricle.

* P < 0.05, †P < 0.005, and ‡P < 0.001, respectively, comparing PGI₂ and PGE₂ vs. saline or PGE₁ groups.
FIGURE 3 Infarct size was directly related to the size of the occluded bed. Linear regressions of infarct mass as percent of left ventricle (LV) vs. occluded bed mass as percent of LV are shown: saline, PGE\(_2\), and PGE\(_1\) in panel A; PGI\(_2\) in panel B. Broken lines in panel B show saline, PGE\(_1\), and E\(_2\) regressions for comparison. PGE\(_1\) and PGI\(_2\) altered the slope of the relation seen in saline controls, so that there was less infarct for similar occluded beds. There was no infarct for occluded bed size less than 21% LV in controls. With PGI\(_2\), the intercept is displaced rightward to 24% LV (NS), and three dogs with occluded beds between 30 and 36% had no infarction. With PGE\(_1\), the intercept is displaced rightward to 26.3% LV (P < 0.05), and one dog with an occluded bed of 34% had no infarction. The relation with PGE\(_2\) was similar to that in controls and the slope was significantly greater than that for PGE\(_1\) and PGI\(_2\).

FIGURE 4 Reconstructed maps showing the spatial geometry of the infarct within the occluded bed, from base (ring 1) to apex (ring 5) of the left ventricle for the saline, PGE\(_2\), PGE\(_1\), and PGI\(_2\) (prostacyclin) groups. Boxes represent scaled maps of mean occluded bed in each ring. Each point represents average data from all infarcted hearts within each group (see Fig. 1). Infarct mass as percent of occluded bed is indicated by numbers (mean ± SEM) within the infarcts (stippled). In all four groups, occluded beds and infarcts taper to the apex. PGE\(_1\) and PGI\(_2\) increased the area of myocardial salvage within the occluded bed in all rings of the left ventricle. This effect was not found with PGE\(_2\).
the infarct:occluded bed ratio in all LV rings from base to apex was markedly less (P < 0.001) with PGI1 than controls (e.g., basal ring 1, PGI1: 19 ± 4% vs. control 47 ± 5%, apical ring 5, PGI1: 8 ± 3% vs. control 26 ± 8%; middle ring 3, PGI1: 12 ± 2% vs. control 40 ± 6%). The absolute mass of infarct was also less (P < 0.05) with PGI1 than controls in corresponding LV rings from base to apex, the respective values being: ring 1: 16 ± 0.4 g vs. 4.7 ± 0.6 g; ring 2: 1.6 ± 0.3 g vs. 4.3 ± 0.5 g; ring 3: 1.1 ± 0.3 g vs. 3.2 ± 0.7 g; ring 4: 0.6 ± 0.2 g vs. 2.2 ± 0.7 g; ring 5: 0.4 ± 0.2 g vs. 1.0 ± 0.4 g. By comparing the reconstructed spatial maps in Figure 4, we found that the amount of uninfarcted myocardium in the occluded bed was greater (P < 0.05) with PGI1 and PGE1 than with controls in both lateral and subepicardial directions of the occluded bed in all LV rings. In Figure 4, the measurements of the thickness of uninfarcted myocardium within the occluded bed for PGI1 and control groups were, re-

Table 3  Regional Myocardial Blood Flow (ml/min per g) in Inner and Outer Layers of the Occluded Coronary Bed in Dogs with Infarcts from the Four Groups

<table>
<thead>
<tr>
<th>Site</th>
<th>Timing</th>
<th>Inner</th>
<th>Outer</th>
<th>Inner</th>
<th>Outer</th>
<th>Inner</th>
<th>Outer</th>
<th>Inner</th>
<th>Outer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct center</td>
<td>Pre-occlusion</td>
<td>0.91</td>
<td>0.79</td>
<td>0.90</td>
<td>0.90</td>
<td>0.96</td>
<td>0.95</td>
<td>0.93</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>± 0.07</td>
<td>± 0.08</td>
<td>± 0.07</td>
<td>± 0.07</td>
<td>± 0.09</td>
<td>± 0.10</td>
<td>± 0.11</td>
<td>± 0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>0.04</td>
<td>0.11</td>
<td>0.04</td>
<td>0.12</td>
<td>0.04</td>
<td>0.10</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>± 0.04</td>
<td>± 0.03</td>
<td>± 0.01</td>
<td>± 0.02</td>
<td>± 0.01</td>
<td>± 0.02</td>
<td>± 0.01</td>
<td>± 0.02</td>
<td></td>
</tr>
<tr>
<td>Infarct margin</td>
<td>Pre-occlusion</td>
<td>0.89</td>
<td>0.82</td>
<td>0.92</td>
<td>0.88</td>
<td>1.01</td>
<td>0.92</td>
<td>0.91</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>± 0.06</td>
<td>± 0.08</td>
<td>± 0.07</td>
<td>± 0.06</td>
<td>± 0.11</td>
<td>± 0.12</td>
<td>± 0.11</td>
<td>± 0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>0.12</td>
<td>0.20</td>
<td>0.13</td>
<td>0.23</td>
<td>0.12</td>
<td>0.18</td>
<td>0.13</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>± 0.03</td>
<td>± 0.03</td>
<td>± 0.02</td>
<td>± 0.03</td>
<td>± 0.02</td>
<td>± 0.03</td>
<td>± 0.02</td>
<td>± 0.02</td>
<td></td>
</tr>
<tr>
<td>Border region</td>
<td>Pre-occlusion</td>
<td>0.95</td>
<td>0.89</td>
<td>0.94</td>
<td>0.86</td>
<td>1.06</td>
<td>0.95</td>
<td>0.98</td>
<td>0.88</td>
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<td></td>
<td>± 0.04</td>
<td>± 0.06</td>
<td>± 0.05</td>
<td>± 0.06</td>
<td>± 0.12</td>
<td>± 0.13</td>
<td>± 0.12</td>
<td>± 0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>0.42</td>
<td>0.57</td>
<td>0.36</td>
<td>0.47</td>
<td>0.45</td>
<td>0.60</td>
<td>0.32</td>
<td>0.42</td>
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<tr>
<td></td>
<td>± 0.04</td>
<td>± 0.06</td>
<td>± 0.04</td>
<td>± 0.04</td>
<td>± 0.09</td>
<td>± 0.1</td>
<td>± 0.05</td>
<td>± 0.05</td>
<td></td>
</tr>
<tr>
<td>Non-risk LAD Center</td>
<td>Pre-occlusion</td>
<td>1.00</td>
<td>1.04</td>
<td>1.06</td>
<td>0.92</td>
<td>1.23</td>
<td>1.06</td>
<td>1.00</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>± 0.07</td>
<td>± 0.11</td>
<td>± 0.08</td>
<td>± 0.06</td>
<td>± 0.16</td>
<td>± 0.12</td>
<td>± 0.09</td>
<td>± 0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-occlusion</td>
<td>0.97</td>
<td>1.07</td>
<td>0.98</td>
<td>0.87</td>
<td>1.20</td>
<td>1.12</td>
<td>0.88</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>± 0.08</td>
<td>± 0.10</td>
<td>± 0.08</td>
<td>± 0.09</td>
<td>± 0.11</td>
<td>± 0.14</td>
<td>± 0.06</td>
<td>± 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. The number of samples pooled in inner or outer halves of each region for the saline, PGE1, PGE2, and PGI1 groups were, respectively: infarct center, 49, 42, 40, 39; infarct margin, 98, 82, 80, 78; border region, 90, 80, 71, 78; LAD region, 50, 43, 40, 66.

* P < 0.001, refers to significance of differences between pre-occlusion and 30 sec post-occlusion flows within a subgroup by paired t test.

† P < 0.05, refers to significance of the differences between 20 sec and subsequent post-occlusion flows by analysis of variance with orthogonal breakdown of the time factor.
Regional Myocardial Blood Flow (RMBF)

Flow data were available in 52 of the 58 dogs killed at 2 days (13, saline; 18, PGI2; 12, PGE1; 9, PGE2) because flows from 6 of the original 58 (2, saline; 1, PGI2; 1, PGE1; 2, PGE2) were excluded due to arrhythmias during flow measurements. In 10 of these 52 dogs which had small or no infarcts (0-2 g, 0-2% LV), the flows were analyzed separately (2, saline; 5, PGI2; 2, PGE1; 1, PGE2). The changes in RMBF in the remaining 42 dogs with visible infarcts (>2 g, >2% LV) are summarized in Table 3.

Flow decreased (P < 0.001) throughout the occluded bed after coronary occlusion in all dogs. In the 42 dogs with visible infarcts (Table 3), flow in the inner central region of the occluded bed decreased by 93%, from 0.92 ± 0.04 to 0.04 ± 0.01 ml/min per g. There was a gradient of collateral flow from central to lateral regions of the occluded bed, and epicardial flows exceeded endocardial flows in the saline group with visible infarcts, collateral flow increased in the first 15 minutes but did not change between 15 minutes and 6 hours by analysis of variance. This trend was highly significant in both inner and outer layers of the infarct center and infarct margin regions (P < 0.005). In the border region of the occluded bed, the trend was similar but statistically less significant in inner (P < 0.01) and outer regions (P < 0.05). A similar observation has been made previously in the same model (Judd et al, 1979d). In the PGE2 group, collateral flow at 20 seconds post-occlusion was similar to that in the control group but did not change significantly by 15 minutes, 1 hour, or 6 hours in infarcted and non-infarcted regions of the occluded bed. In contrast, PGE1 and PGI2 groups had significantly different (P < 0.05) flows from those for PGE2 and saline groups.

Figure 5 Mean values for collateral blood flow at 20 seconds, 15 minutes, 1 hour, and 6 hours after occlusion in transmural samples from infarct center (C), infarct margin (M), and border regions (B) in saline control, PGE1, PGE2, and PGI2 groups. Treatments were begun between 20-second and 15-minute measurements. The significance of difference of value vs. time within each group using analysis of variance is denoted by asterisks (*P < 0.05, **P < 0.01). The 20-second value in border regions for PGE1 or PGI2 was different from saline and PGE2 groups (P < 0.05) by multiple comparisons least significant difference test; by the same test, 6-hour values in center and margin regions for PGE1 or PGI2 groups were significantly different (P < 0.05) from those for PGE2 and saline groups.
in the four groups were not significantly different by 6 hours (Table 3). The transmural flows (ml/min per g) in the four groups at 15 minutes and 6 hours in the infarct center were: saline, 0.11 ± 0.01 vs. 0.11 ± 0.02 (NS); PGE₂, 0.08 ± 0.02 vs. 0.09 ± 0.03 (NS); PGE₁, 0.17 ± 0.02 vs. 0.29 ± 0.04 (P < 0.05); PGI₂, 0.23 ± 0.05 vs. 0.31 ± 0.06 (P < 0.05). Corresponding transmural flows in the infarct margin were: saline, 0.20 ± 0.03 vs. 0.22 ± 0.04 (NS); PGE₂, 0.20 ± 0.05 vs. 0.23 ± 0.05 (NS); PGE₁, 0.28 ± 0.04 vs. 0.36 ± 0.04 (P < 0.05); PGI₂, 0.32 ± 0.05 vs. 0.47 ± 0.08 (P < 0.05); (Fig. 5). With PGI₂, collateral flow increased more markedly in nine dogs than in the four other dogs. Flow changes in the LAD region were not significantly different in the three treatment groups. The calculated changes in regional coronary vascular resistance paralleled those in RMBF among the four groups.

In view of the recent recognition that microsphere flows in infarcted regions may be artificially reduced because of varying degrees of microsphere loss and/or tissue swelling (Capurro et al., 1979; Jugdutt et al., 1979c; Reimer et al., 1979), the changes in collateral flow in the 42 dogs with visible infarctions were re-analyzed after correction for microsphere loss and/or tissue swelling (Capurro et al., 1979; Jugdutt et al., 1981). The values of the ratios of the pre-occlusion microsphere content to that in the non-ischemic LAD bed (Murdock and Cobb, 1980; Jugdutt et al., 1981). The values of the ratios were less than the expected value of 1.0; the deviation from unity is caused by a combination of tissue swelling, cellular infiltrate, and microsphere loss (Jugdutt et al., 1979c). In the 10 dogs with small or no infarcts, five (2, saline; 1, PGI₂; 1, PGE₁; 1, PGE₂) had small occluded beds (18.5 to 26.5% LV), and the collateral flows were high post-occlusion. Thus, the pre-occlusion, 20-second, and 6-hour post-occlusion endocardial flows in the center of the occluded bed were: 1.20 ± 0.17, 0.69 ± 0.16, and 0.67 ± 0.09 ml/min per g, respectively. In one other dog that received PGE₁, the occluded bed was 33.5% LV but there was no infarct; endocardial flows in the center of the occluded bed were 0.73, 0.18, and 0.51 ml/min per g preocclusion, 20 seconds and 6 hours post-occlusion, respectively. The remaining four dogs were treated with PGI₂; their occluded beds ranged from 30.5 to 33.5% LV, and none had infarcts. Endocardial flows in the center of the occluded bed in these dogs were: 0.91 ± 0.10, 0.33 ± 0.12, and 0.65 ± 0.14 ml/min per g pre-occlusion, 20 seconds and 6 hours post-occlusion, respectively.

In order to gain insight into the mechanism for myocardial protection by PGI₂ and PGE₁, we related the amount of collateral flow in the center of the occluded bed 6 hours after occlusion to the amount of myocardial salvage within the occluded bed (Fig. 6). Inspection of Figure 6 reveals that for hearts treated with PGI₂ and PGE₁, the data points mostly grouped downward and to the left, indicating low collateral flow and no myocardial salvage. The one PGE₂ heart with apparent salvage (91%) had a small risk region. Three of the four hearts (one from each treatment group) with 100% salvage had small occluded regions and high flow.

**Figure 6** Transmural collateral blood flow in the center of the occluded bed at 6 hours post-occlusion was related directly to the amount of myocardial salvage within the occluded coronary bed. PGI₂ and PGE₁-treated hearts are shifted upward and to the right, indicating both greater salvage and higher collateral flow. In addition, marked salvage is seen with PGE₁ and PGI₂ despite low collateral flow, suggesting that protection by PGE₁ and PGI₂ was in part due to mechanisms other than flow. The PGE₂ hearts are mostly grouped downward and to the left, indicating low collateral flow and no myocardial salvage. The one PGE₂ heart with apparent salvage (91%) had a small risk region. Three of the four hearts (one from each treatment group) with 100% salvage had small occluded regions and high flow.
are shifted upward and to the right, indicating both greater myocardial salvage and higher collateral flow. However, in some hearts, marked salvage was seen with PG" and PGE, despite low levels of collateral flow at 6 hours. Thus in Figure 6, using flow of 0.30 ml/min per g as an arbitrary cut-off value, 9 hearts with PG" had flow below this value while the other 9 hearts had flow above this value. In controls, 10 of the 13 hearts had 6-hour flows below 0.30 ml/min per g in the center of the occluded bed. This suggests that protection by PG" and PGE, may have, in part, been related to mechanisms other than the increased flow. In contrast, data for the PGE, hearts were mostly displaced downward and to the left, indicating lesser myocardial salvage and collateral flow. In one PGE, heart with apparent salvage (91%), the occluded bed was small (23.8% LV) and collateral flow at 6 hours was 0.26 ml/min per g in the infarct center and 0.47 ml/min per g in the infarct margin.

Histology

Histological examination confirmed necrosis in samples from infarcted regions in all hearts. Hemorrhage and inflammatory cells were not quantified. Inner halves of infarct center and margin regions had 100% histological necrosis. The outer halves of infarct center and margin regions had 55% and 20% histological necrosis, respectively. Border samples in both groups were visually normal and no necrosis was found in any of the 84 examined histologically.

Discussion

The two major findings in this study are as follows. First, both PG" and PGE, reduced infarct size after permanent coronary occlusion in the conscious dog, but PGE, was not beneficial. These dissimilar effects were associated with similar percentage reductions in mean arterial and mean left atrial pressures and no change in heart rate. The mass of infarcted myocardium within the occluded bed was reduced throughout the left ventricle, with sparing in both epicardial and lateral regions. Second, collateral blood flow increased markedly over the 6-hour infusion period with PG" and PGE, but did not change with PGE2. At the end of this period, flow in the infarct center and margin was approximately 2- to 3-fold greater in the PGE and PGE, groups than in control and PGE2 groups.

It has recently been recognized that microsphere flow measurements in areas of myocardial infarction may be artificially reduced because microspheres injected before coronary occlusion are lost from necrotic areas compared to non-ischemic regions (Capurro et al., 1979; Jugdutt et al., 1979c). In our study, microsphere loss in infarcted regions, as judged by the reduction in pre-occlusion microsphere content relative to that in the non-ischemic LAD area, was seen in all four treatment groups. We handled all four treatment groups similarly and measured flows over a limited period of 6 hours post-occlusion, 42-48 hours before sacrifice. It is likely that microspheres injected over this short period of time would be lost to a similar extent, making comparison of relative differences in flow over that interval between groups valid. The apparent loss of microspheres in the center of the infarct region, as judged by the reduction in pre-occlusion microsphere content relative to that in the non-ischemic LAD area (Murdock and Cobb, 1980), was about 17% in the control group, 16% in the PGE, group, 8% in the PGE, group, and 6% in the PG" group. The lesser microsphere loss in PG" and PGE, dogs may have been related to its beneficial effects on myocardial necrosis or a decrease in edema in infarcted tissue. However, correction for microsphere loss confirmed the trends in sequential post-occlusion flows found in the uncorrected data among all four treatment groups. This method of correction for flows assumes similar loss of pre- and post-occlusion microspheres, but appears reasonable since microspheres were injected over 6 hours and the animals killed 42 hours later.

Two further comments must be made about this study. First, the mean arterial pressures pre-occlusion were higher than reported in some other studies with conscious dogs (Rivas et al., 1976) probably because, unlike those investigators, we did not train the dogs to stand quietly in the laboratory. However, all four groups of dogs were treated in identical fashion. Second, we began therapy as early as possible post-occlusion (5 minutes) in order to optimize the effect of therapy on ischemic myocardium so that we might have measured the first post-occlusion flow before a "steady state" was reached (Rivas et al., 1976) in all four groups.

The reason for the continued increase in collateral flow over the first six hours with PG" and PGE, is not immediately obvious in our study. Since vessels in the occluded bed are believed to become maximally dilated soon after occlusion, it is not clear why further dilation of collateral vessels should occur with PG" and PGE, (Schaper et al., 1976). Initially, exogenous PG" and PGE, may have increased collateral flow because of direct dilatory effects on the coronary circulation. The reduction in extravascular compressive forces due to reduced left ventricular filling pressure is an unlikely explanation because the filling pressure was also reduced with PGE, but collateral flow did not increase. PG" and PGE, may have acted directly on collateral vessels in the occluded bed (although they are generally believed to be incapable of vasodilation), vessels in the occluded bed which may not have been maximally vasodilated, or vessels within the unoccluded bed directly feeding the collaterals. Ad-
ditional increases in collateral flow over the 6-hour infusion period may have been related to myocardial protection by PGI₂ and PGE₁. With reduction in tissue necrosis and/or edema, delayed increases in flow may have been possible through progressive mechanical stretching of collateral channels or progressive build-up of other vasoactive substances. PGI₂ and PGE₁ may also have relieved the vasoconstriction or vasospasm (Kalsner, 1975; Needleman et al., 1978) which develops in vessels within the occluded bed (Steenbergen et al., 1977).

In this study, we found close linear relationships between infarct size and the size of the occluded coronary bed. As in previous studies using this model (Jugdutt et al., 1979a, 1979b), the extrapolated horizontal axis intercept for control animals was about 20 g or 20% LV mass, indicating that no infarction developed when occluded beds were smaller than this size. This lack of infarction in small occluded beds is probably explained by the high levels of collateral flow found post-occlusion. In this model, a change in infarct size is reflected in a significant change in the slope of linear regression between infarct mass and the mass of the occluded bed. We have found this model to be sensitive for assessing effects of interventions on infarct size, and have demonstrated an increase in infarct size with indomethacin (Jugdutt et al., 1979a) and decreases with ibuprofen and nitroglycerin (Jugdutt et al., 1980, 1981). In all these experiments, the regional distribution of necrosis corresponded to a gradient of collateral flow from peripheral to more central regions of the occluded bed (Jugdutt et al., 1979d). Although the non-infarcted lateral border regions were well within the arteriographically defined boundaries of the occluded bed and had diminished flows and reduced inner/outer flow ratios post-occlusion, we cannot completely exclude the possibility that the border samples might have contained some normal tissue from the unoccluded beds and thus partially explain the higher flows in this region.

Several mechanisms could explain the beneficial effects of PGI₂ and PGE₁ on infarct size. Myocardial salvage could have been due to a reduction in myocardial oxygen demands associated with the 5 to 11% decrease in arterial pressure, although this would not appear to have been a major factor since the 10% decrease in arterial pressure with PGE₂ was not associated with salvage. The increase in collateral blood flow is likely to have played a major role. Significant increases in flow were found throughout the 6-hour infusion period with both PGI₂ and PGE₁. At the end of this time, collateral flow was 2- to 3-fold higher in the PGI₂ and PGE₁ groups compared to PGE₂ and control groups. In the four PGI₂ dogs with large increases in flow to central regions of the occluded bed, there was virtually complete salvage. In other dogs where collateral flow did not increase as much, and was less than 0.3 ml/min per g in the center of the occluded bed by 6 hours (PGI₂, nine dogs; PGE₁, five dogs), infarction occurred but was less extensive compared to controls (Fig. 6). The fact that myocardial salvage occurred in some dogs with low levels of collateral flow suggests that factors other than flow might also be important. In these dogs, PGI₂ and PGE₁ may have maintained cellular viability until later increases in collateral circulation developed, beyond the 6-hour period (Schaper and Pasyk, 1976).

Non-flow mediated myocardial salvage may have been due to several beneficial cellular and metabolic effects of PGI₂ and PGE₁. First, trapping of platelets, which occurs in ischemic regions, has been suggested as a reason for evolving necrosis in the marginal zones of infarcts, and inhibitors of platelet aggregation, such as aspirin and dipyridamole, have been shown to reduce ischemic injury and infarct size (Haft et al., 1972; Kraikippanitch et al., 1976, Ruf et al., 1980). Platelet aggregation is accompanied by secretion of granular constituents which include coagulation factors, vasoconstrictors, and other substances that promote further aggregation and thrombus formation (Packham and Mustard, 1977). Platelet clumps may therefore interfere with collateral development and function in ischemic regions, and initiate a vicious cycle of plug formation, vasoconstriction, thrombosis and more necrosis. PGE₁ is a potent inhibitor of platelet aggregation and thrombus formation in vivo (Emmons et al., 1967) and may protect ischemic tissue via this mechanism. PGI₂ not only is a potent inhibitor of platelet aggregation but also causes a disaggregation of clumped platelets, presumably by augmenting cyclic AMP levels (Moncada et al., 1976; Dusting et al., 1977; Whittle et al., 1978). In addition, platelets convert endoperoxides to thromboxane A₂, which is a potent platelet aggregator and coronary vasoconstrictor (Ellis et al., 1976). Unlike PGI₂, thromboxane A₂ has not been shown to be synthesized in coronary arteries (Raz et al., 1977), but endothelial vessel injury in the ischemic region could expose collagen to platelets and favor platelet deposition and thrombosis (Needleman and Kaley, 1978). Since PGI₂ synthesis may be reduced in damaged endothelium in ischemic regions and allow thrombus formation (Needleman and Kaley, 1978), exogenous PGI₂ and PGE₁ may be beneficial under these circumstances and partly antagonize the harmful effects of thromboxane A₂.

Second, leukocytes and other inflammatory cells that become trapped in the occluded coronary bed (Sommers and Jennings, 1964) release lysosomal enzymes, such as acid hydrolases and proteases (Brachfeld 1969; Lefer et al., 1974; Nakamshi et al., 1975; Kennett et al., 1978) which normally assist in phagocytic functions of polymorphs. These lysosomal enzymes may also harm non-ischemic cells in the occluded bed (Brachfeld, 1969). Both PGI₂ and PGE₁ have been shown to stabilize lysosomes in cardiac cells (Ogletree and Lefer, 1978a) and may have similar effects on lysosomes in phagocytic...
cells, thereby preventing release of harmful lysosomal enzymes. In addition, PGI₂ has been shown to stimulate the adrenal glands to release corticosteroids (Ellis et al., 1978), and could act via this mechanism to produce beneficial effects attributed to corticosteroids, such as a decrease in inflammatory cell infiltration (Wiener et al., 1975), stabilization of lysosomal membranes in ischemic cardiac cells (Spaeth et al., 1974; Weiseman et al., 1975; Fox et al., 1978) and polymorphs (Nakanishi et al., 1975) and the inhibition of the released lysosomal enzymes (Smith et al., 1976). However, we did not quantify inflammatory cell infiltrate in this study. Third, since PGE₁ inhibits the release of norepinephrine from myocardial nerve terminals on cardiac sympathetic nerve stimulation (Samuelsson et al., 1971), it might counteract the harmful effects of increased catecholamine release during myocardial ischemia. The antiarrhythmic effect of PGE₁ (Kelhiher et al., 1973) during myocardial ischemia might also result from its antagonism of the cycle of increased catecholamines, increased circulating free fatty acids, increased myocardial metabolism, and arrhythmogenesis. Finally, Kury et al., (1974) found that PGE₂ enhances red blood cell deformability and may thus promote oxygen delivery to ischemic myocardium.

Beneficial effects of PGE₁ on ischemic myocardium have been found by other investigators in both dogs and cats. Thus, PGE₁ increased collateral blood flow in anesthetized cats (Hutton et al., 1973) and dogs (Takano et al., 1977). Mjos et al. (1976) found that PGE₁ reduced ischemic injury, measured by ST-segment elevation, in anesthetized dogs. Ogletree and Lefer (1978a) demonstrated marked myocardial protection (measured by ST-segment elevation, myocardial creatine phosphokinase (CPK), myocardial lysosomal hydrolases, cathepsin D, and β-glucuronidase) with intravenous PGE₁ after coronary occlusion in anesthetized cats. In this latter study, the investigators reported intermediate protection with PGE₂ and none with PGF₂α. Since PG's have different effects in different species, the dissimilar effects of PGE₁ and PGE₂ on infarct size in our study and in that of Ogletree et al. (1978a) are not entirely surprising. Structural differences between PGE₁ and PGE₂ may be important, since PGE₁ contains one double bond and is derived from dihomo-γ-linolenic acid, whereas PGE₂ contains two double bonds and is derived from arachidonic acid. PGE₁ is a more potent coronary dilator than PGE₂ in several animal species (Strong et al., 1967; Hedqvist et al., 1971; Kalaner, 1975; Boroyan, 1976; Needleman et al., 1978). PGE₂ has been reported to contract isolated strips of canine, bovine, and human coronary arteries (Dusting and Vane, 1980). Ogletree et al. (1978b) reported that PGE₂ produced dose-dependent coronary arterial constriction in the cat, whereas Ushida et al. (1977) reported cyclical coronary spasm with PGE₂ in anesthetized dogs. Although PGE₂ produced a small increase in collateral blood flow to ischemic endocardial regions in anesthetized dogs (Kirmser et al., 1977) and prevented the decrease in collateral blood flow after indomethacin, it did not prevent the increased ischemic injury after indomethacin (Wolfson et al., 1977). However, mechanisms other than flow may have resulted in the dissimilar effects of PGE₁ and PGE₂ on the infarction process. Thus, unlike PGE₁, PGE₂ has little inhibitory effect on platelet aggregation (Weeks et al., 1969) or thrombosis (Emmons et al., 1967) and makes erythrocytes "less deformable" so that oxygen delivery to ischemic myocardium is not promoted (Kury et al., 1974). A further possibility is that PGE₁ and PGE₂ may differ in their ability to protect lysosomal membrane.

The protective effect of PGI₂ on ischemic myocardium is not confined to the dog. Ogletree et al. (1979) have recently demonstrated the protective effect of PGI₂ infusion (5 nmol/kg per min intravenously) over 5 hours after coronary occlusion in anesthetized cats. Untreated cats in their study showed ST-segment elevation, significant loss of CPK from ischemic relative to normal tissue, and loss of the lysosomal protease cathepsin D. In contrast, PGI₂-treated cats showed no ST-segment elevation, no significant loss of ischemic tissue CPK, and no loss of cathepsin, suggesting that PGI₂ maintained cellular integrity and prevented lysosomal disruption. In addition, they found that PGI₂ produced a sustained fall in mean arterial pressure without a change in heart rate, suggesting diminished myocardial oxygen demands, and demonstrated that PGI₂ inhibited platelet aggregation during myocardial ischemia. Although PGI₂ is a potent coronary vasodilator (Dusting et al., 1977 and 1980; Raz et al., 1977), it also dilates other systemic arteries. Marked hypotension may jeopardize coronary perfusion. Thus, other investigators found no change (Ribeiro et al., 1979) or a decrease (Jentzer et al., 1979) in collateral flow in anesthetized dogs, but in each of these studies PGI₂ produced a fall in mean arterial pressure of about 15–45% which might have diminished driving pressure for collateral flow. It is interesting to note that the dose of PGI₂ used in these studies was similar to ours, suggesting that an increased vasodilator effect may occur during anesthesia. Alternatively, the prolonged infusion times utilized in our study may have permitted partial metabolic inactivation of PGI₂ to occur in the infusion syringe, resulting in a lower-than-calculated administered dose. This factor might also explain why PGI₂ did not have a markedly greater effect on myocardial salvage than PGE₁. Recently, Araki and Lefer (1980) demonstrated in the perfused cat heart that PGI₂ protected ischemic myocardium even without its effects on coronary vasodilation and inhibition of platelet aggregation.

Our findings with PGI₂ and PGE₁ in conscious dogs cannot be extrapolated directly to humans without further critical studies to determine suitability of these substances for clinical trials in myo-
cardiac infarction. There are several reasons to believe that PGI₂ might be applicable in human infarction, apart from our findings in the conscious dog. First, PGI₂ is synthesized in human arterial wall (Moncada et al., 1977) and the coronary vasodilator and platelet inhibitory effects of exogenous PGI₂ may be beneficial in human infarction where coronary spasm and thrombosis are thought to play an important role. Second, the lysosomal membrane stabilization effect of PGI₂ may be useful in patients with acute myocardial infarction, since stabilization with methylprednisolone of lysosomal membranes in such patients was recently found to be associated with a delay in tissue damage (Welman et al., 1979). Third, intravenous administration of PGI₂ to healthy human subjects was associated with minimal side-effects at low doses (2-5 ng/kg per min), although a dose-related hypertension was seen at higher doses (50 ng/kg per min) (Szczeklik et al., 1978). However, as with other vasodilators, the dose could be adjusted to avoid serious hypertension. Although PGI₂ was given into the left atrium in our study, the effects of left atrial and intravenous administration would be expected to be similar since PGI₂ is not inactivated in the lung (Armstrong et al., 1977; Needleman et al., 1978; Dusting et al., 1978) and may in fact be a "circulating hormone" (Moncada et al., 1978; Dusting and Vane, 1980). Nevertheless, further studies in animals are needed to assess the effects of PGI₂ in the presence of simulated multivessel coronary artery disease, as would be found in humans, and to determine the effects of delaying therapy after coronary occlusion on myocardial salvage. Few reports have described the use of PGE₁ in infants, to reverse the constriction of the patent ductus arteriosus and increase pulmonary blood flow (Elliott et al., 1975).

In summary, we have shown that PGI₂ and PGE₁, given after coronary occlusion in the conscious dog decreased infarct size, but PGE₂ did not have a beneficial effect. Although decreased myocardial oxygen demands associated with the mild reduction in arterial pressure may have contributed partially to the protective effect of PGI₂ and PGE₁, it did not result in significant protection in PGE₂-treated dogs. Myocardial salvage by PGI₂ and PGE₁ appeared to have been related in major part to increases in collateral blood flow. Since myocardial salvage occurred in some dogs despite low levels of flow, metabolic and cellular effects may also have played an important role in the protective effect of these two PGs on ischemic myocardium.

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