The Interaction of Platelets With Aortic Subendothelium: Inhibition of Adhesion and Secretion by Prostaglandin I\(_2\)

By Burt Adelman, Michael B. Stemerman, Deborah Mennell, and Robert I. Handin

We have studied the effect of prostaglandin I\(_2\) on platelet turnover, attachment to the subendothelium, and secretion following balloon deendothelialization of the rabbit aorta. Survival of \(^{51}\)Cr-labeled platelets in the balloon-injured animals remained normal. Thirty minutes after injury, there were \(4.52 \times 10^8\) platelets/sq cm attached to the aortic surface, which was 87% covered by platelets. Although plasma platelet factor 4, as measured by radioimmunoassay, did not rise above the normal level of \(6.8 \pm 2.6\) ng/ml (mean \pm SEM) during the first hour after balloon injury, platelet factor 4 antigen was detected within the vessel wall by indirect immunofluorescence.

Platelets secrete a mitogenic protein that promotes smooth muscle cell growth in culture and may initiate in vivo proliferation of smooth muscle cells.\(^1\)\(^2\) Although small quantities of this platelet-derived growth factor (PDGF) have been purified from human platelets,\(^3\) it has not been possible to measure and localize the PDGF, which is presumably secreted after platelets have adhered to exposed subendothelium. To study the secretion of platelet proteins in vivo, we have developed an immunofluorescent technique and radioimmunoassay for human\(^4\) and rabbit platelet factor 4 (PF-4), a closely related \(\alpha\)-granule protein. With these assays, we have previously detected platelet \(\alpha\)-granule secretion in patients with ischemic cardiovascular disease\(^5\)\(^6\) and have localized PF-4 within the rabbit aorta following balloon deendothelialization.\(^6\)

Release of the PDGF following platelet adhesion to the injured aortic surface is thought to initiate vascular smooth muscle cell proliferation, since severely thrombocytopenic animals do not develop myointimal thickening after balloon deendothelialization\(^7\) or other forms of arteriointimal injury.\(^8\) In the present study, we document that PF-4 enters the vessel wall following balloon deendothelialization of the rabbit aorta and within 30 min of injury. An infusion of 650–850 ng/kg/min prostaglandin I\(_2\) completely inhibited platelet aggregation and reduced surface coverage by 84% and platelet attachment by 63%. Animals given 50–100 ng/kg/min prostaglandin I\(_2\), which only partially inhibited platelet aggregation, had 70% of the aortic surface covered by platelets. Platelet factor 4 antigen was also detected within the aortic wall. Platelet attachment was normal in animals that had been given 850 ng/kg/min prostaglandin I\(_2\) prior to balloon injury but sacrificed after the infusion was stopped and ex vivo platelet aggregation had returned to normal.

Materials and Methods

Materials

Male New Zealand white rabbits weighing 2.8–3.2 kg were obtained from ARI Breeding Laboratories, Avon, Mass., and allowed free access to rabbit chow and water. PG\(_1\) was kindly supplied by Dr. John Pike of the Upjohn Company, Kalamazoo, Mich. Embedding medium for frozen sections was a commercially prepared material containing water-soluble glycols and resins, Ames OCT compound (Fisher Scientific Co., Medford, Mass.). Adenosine diphosphate (ADP) was obtained from Sigma Chemicals, St. Louis, Mo., and acid-soluble collagen from Hormon-Chemie, Munich, Germany. Fluorescein-conjugated rabbit antiserum IgG was obtained from Cappel Laboratories, Cochranville, Pa. The Na\(_2\)\(^{131}\)CrO\(_4\) used for labeling of platelets and carrier-free Na\(^{125}\)I used for iodination of PF-4 were from New England Nuclear, Boston, Mass. Chloramine T was obtained from Eastman-Kodak, Rochester, N.Y. All other chemicals were reagent grade obtained from standard distributors.

Platelet Counts

Platelet counts on platelet-rich plasma (PRP) were performed on a Coulter Counter Model F (Coulter, Hialeah, Fla.). When platelet counts were performed on whole blood, the technique outlined by Brecher et al. was followed.\(^8\)

Platelet Aggregation

Platelet aggregation studies were performed on PRP obtained from whole blood drawn into one-tenth volume 3.8% sodium citrate and centrifuged at 300 g at room temperature for 10 min, using a standard nephelometric technique.\(^9\) Aliquots of PRP were warmed to 37°C and stirred at 800 rpm in a Chronolog dual-channel aggregometer (Chronolog Corp., Broomall, Pa.). The final concentration of ADP was 2.9 \(\mu\)M, and of collagen 12.5 \(\mu\)g/ml.
Preparation of \(^{51}\)Cr-Labeled Platelets

Blood was collected by ear-vein cannulation into 1 ml ACD (NIH Formula A) per 5 ml whole blood. PRP was obtained by centrifugation and the pH adjusted to pH 6.5, with additional ACD. The acidified platelets were then centrifuged at 200 g for 15 min at room temperature and the platelet pellet resuspended in 1 ml of a Ringer-Citrate-Dextrose solution made up of 7 parts Krebs-Ringer phosphate, 2 parts 3.12% sodium citrate, and 1 part 5% dextrose. To this 1-ml suspension of platelets, 100 \(\mu\)Ci of Na\(^{51}\)CrO\(_4\) were added and the suspension allowed to incubate at 37\(^\circ\)C for 30 min in a shaker bath. After incubation, the platelets were again centrifuged at 2000 g for 10 min and washed twice with autologous platelet-poor plasma (PPP). The platelets were then resuspended in 4 ml of PPP for injection.

Balloon Deendothelialization and Arterial Blood Sampling

The right iliac and entire aorta of each animal was denuded of endothelium according to a modification of the Baumgartner balloon deendothelialization method. After endothelial cell removal, the femoral artery was kept occluded by a taut loop of 4-0 silk. By loosening this loop, the artery could be reentered with a cannula for blood drawing.

Purification of PF-4

PF-4 was isolated by our previously published technique developed for human material. The protein peak eluting at 1.2 M NaCl contained 90% of the applied heparin-neutralizing activity, migrated as a single band on 7.5% polyacrylamide gels in the presence of 0.2% SDS and 1 mM DTT, and had an estimated molecular weight of 8000. Each milligram of the purified material neutralized 210 U of heparin.

Immunoassay of Rabbit PF-4

Our technique for the production of a sheep anti-rabbit PF-4 antibody has been previously described. Ten micrograms of PF-4 were iodinated with the chloramine T technique. The specific activity of the labeled product was between 40 and 50 \(\mu\)Ci/g PF-4:

\[ \text{activity of the labeled product was between 40 and 50 } \mu\text{Ci/g PF-4:} \]

The antibody has been previously described. Ten micrograms of PF-4 were iodinated with the chloramine T technique. The specific activity was estimated to be 57 ml/kg. Thirty minutes after receiving the labeled platelets, animals underwent balloon deendothelialization. A 2-ml specimen of whole blood was collected from an ear-vein immediately prior to injury. Subsequent specimens were collected 30 min and 1 hr after injury and twice daily for 3 days. Radioactivity was determined in a Beckman Gamma 8000 gamma counter (Beckman Instruments, Menlo Park, Calif.). The radioactivity present 30 min after infusion of the labeled platelets and prior to aortic injury was used to calculate both initial platelet recovery and subsequent life-span.

Survival and Adhesion of \(^{51}\)Cr-Labeled Platelets Following Balloon Deendothelialization

For platelet survival studies, each animal was given, via an ear vein, \(4 \times 10^9\) platelets suspended in 2 ml PPP. Fifty microliters of the platelet preparation were saved to calculate platelet recovery, which averaged 77%. Blood volume for the recovery calculation was estimated to be 57 ml/kg. Thirty minutes after receiving the labeled platelets, animals underwent balloon deendothelialization. A 2-ml specimen of whole blood was collected from an ear-vein immediately prior to injury. Subsequent specimens were collected 30 min and 1 hr after injury and twice daily for 3 days. Radioactivity was determined in a Beckman Gamma 8000 gamma counter (Beckman Instruments, Menlo Park, Calif.). The radioactivity present 30 min after infusion of the labeled platelets and prior to aortic injury was used to calculate both initial platelet recovery and subsequent life-span.

For studies of platelet attachment to the vessel wall, each animal was given 8 \(\times\) \(10^9\) labeled platelets suspended in 4 ml PPP. Thirty minutes after balloon deendothelialization, a blood specimen was obtained, and the animals were sacrificed and perfused with cacodylate-glutaraldehyde fixative and the aorta dissected as described above. After fixation, each aorta was opened and pinned out, then cut into circumferential strips measuring 1 cm wide. The area of each strip was measured and its associated radioactivity determined in the gamma counter. By calculating the specific activity of the total platelet mass for each animal (cpm/platelet), it was possible to determine the total number of platelets adherent to each 1-cm wide aortic strip (total number of platelets = counts present/specific activity of platelet mass). These calculations assume that labeled
platelets and nonlabeled platelets attached equally to the subendothelial surface. The difference between the mean values of grouped data was calculated with Student's t test.

**PGI2 Infusion in Rabbits**

A stock solution of PGI2 was made by dissolving the sodium salt in absolute ethanol, 200 ng/μl, and stored for up to 2 wk at -40°C. The stock solution was diluted with 0.1 M Tris-buffer, pH 9.0, and infused into the jugular vein via a 16-gauge plastic catheter connected to a constant-infusion pump (Sage pump model 341, Orion, Cambridge, Mass.). The infusion rate in all experiments was kept constant at 0.31 cc/min, and the dosage of PGI2 was progressively increased. During the infusion period, the syringe and tubing were kept at 4°C. Immediately prior to initiation of the infusion, each animal was given an intravenous infusion of 3 mg/kg aminophylline. Blood specimens for platelet aggregation were drawn from the right femoral artery, which was exposed for balloon deendothelialization. Five minutes after the aminophylline infusion, blood was drawn for aggregation studies and the PGI2 infusion begun. After 30–45 min, a second arterial blood specimen was obtained for repeat aggregation studies. During the dose–response experiments, the PGI2 concentration was increased every 30 min following withdrawal of blood for aggregation studies.

Because 850 ng/kg/min PGI2 consistently produced total inhibition of platelet aggregation, this dose was used in all experiments to achieve maximal platelet inhibition prior to balloon injury. In all studies, however, platelet aggregation was performed on blood drawn just prior to balloon injury. Animals were balloon-injured within 15 min of this second aggregation study, and the PGI2 infusion was continued until the animals were sacrificed 30 min after injury. Thirteen minutes were needed to prepare PRP and carry out the aggregation studies.

In one study, the PGI2 infusion was discontinued 15 min after injury and the animals kept alive until repeat aggregation studies demonstrated that aggregation had returned to normal. Once normal platelet activity had been documented, the animals were sacrificed in the standard fashion for examination of specimens by electron microscopy.

**RESULTS**

**Platelet Kinetics in Balloon-Deendothelialized Rabbits**

The survival of allogeneic 51Cr-labeled platelets given to 4 rabbits 30 min prior to aortic balloon deendothelialization was followed for 70 hr and is shown in Fig. 1. The disappearance of labeled platelets in these injured animals was identical to that found in normal animals. Although there was no measurable decrease in platelet life-span following balloon injury, some of the circulating 51Cr-labeled platelets had attached to the exposed aortic subendothelium 30 min after injury. As shown in Table 1, there was an average of 4.52 ± 0.23 x 10⁶ (mean ± SEM) platelets/sq cm of aorta after balloon injury (n = 4) compared to 2.33 ± 0.58 x 10⁵ platelets/sq cm of aorta in nonballooned animals (n = 4). The number of attached platelets/sq cm of aorta was uniform, with no significant difference noted when comparing thoracic to abdominal aortic segments. There was an average of 7.44 x 10⁷ platelets attached to the entire deendothelialized aorta. Based on an average platelet count of 375,000/μl for the rabbits in the study, the total number of platelets attached to each rabbit aorta is equivalent to the number of platelets present in 0.2 ml of whole blood.

**Detection of PF-4 in the Plasma and Vessel Wall of Balloon-Injured Animals**

The release of PF-4 after vascular injury was followed by measurement of plasma levels and by immunofluorescent staining for PF-4 antigen in the vessel wall. The PF-4 concentration in femoral arterial blood did not increase during the first hour after aortic balloon injury. The initial level, prior to balloon injury, was 6.8 ± 2.6 ng/ml (mean ± SEM) in each of 8 animals (Table 2). Successive aortic blood plasma samples obtained over a 1-hr period after injury had PF-4 levels that were within this normal range.

In contrast, PF-4 was detected by indirect immunofluorescent staining of rabbit aortae following balloon injury. Peak fluorescence (Fig. 2) occurred in animals sacrificed 30 min after injury and was diminished in animals sacrificed 1 or 2 hr after injury. By 3.5 hr after injury, PF-4 could no longer be detected by this

---

**Table 1. Effect of PGI2 Infusion on Platelet Attachment to Balloon-Deendothelialized Rabbit Aorta**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Platelets/sq cm of aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon-injured</td>
<td>4.52 ± 0.23 x 10⁶</td>
</tr>
<tr>
<td>Balloon-injured + PGI2</td>
<td>1.69 ± 0.45 x 10⁶</td>
</tr>
<tr>
<td>(850 ng/kg/min)</td>
<td>2.33 ± 0.58 x 10⁵</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
†p < 0.001.
Table 2. PF-4 Levels in Plasma Following Balloon Deendothelialization*

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>PF-4 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>6.8 ± 2.6</td>
</tr>
<tr>
<td>0</td>
<td>7.7 ± 3.2</td>
</tr>
<tr>
<td>5</td>
<td>6.8 ± 2.6</td>
</tr>
<tr>
<td>10</td>
<td>7.5 ± 2.9</td>
</tr>
<tr>
<td>15</td>
<td>9.5 ± 6.8</td>
</tr>
<tr>
<td>25</td>
<td>7.4 ± 3.1</td>
</tr>
<tr>
<td>35</td>
<td>6.2 ± 2.2</td>
</tr>
<tr>
<td>45</td>
<td>6.4 ± 2.2</td>
</tr>
<tr>
<td>60</td>
<td>8.0 ± 3.9</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

technique; however, adherent platelets remained brightly fluorescent. These results suggest that the adherent platelets do not secrete their entire content of PF-4 at the time of adhesion. In order to demonstrate that PF-4 only entered vessels after endothelial removal, sections through the aortic bifurcation were examined. Consistently, the deendothelialized left iliac artery was brightly fluorescent, while the adjacent right iliac segment, with intact endothelium, did not fluoresce.

Effect of PGI₂ Infusion on Platelet Adhesion and Secretion Following Balloon Deendothelialization

Increasing concentrations of PGI₂ were given until a blood concentration was achieved that caused complete inhibition of platelet aggregation to collagen and ADP. Each animal was also given one injection of 3 mg/kg aminophylline to inhibit platelet phosphodiesterase activity and to prolong the effect of PGI₂. Infusion rates of less than 200 ng/kg/min had little effect on collagen-induced aggregation of PRP, while higher doses progressively inhibited both ADP- and collagen-induced aggregation. However, considerable variation in the degree of inhibition was noted, until a rate of 850 ng/kg/min was reached. This dose caused complete inhibition of ADP- and collagen-induced aggregation in all animals tested.

Transmission electron micrographs and 1-μm sections of aortic tissue from animals given varying amounts of PGI₂ and sacrificed 30 min after balloon injury were examined (Fig. 3). In animals that only received Tris-buffer, a closely adherent layer of spread platelets was seen along the entire subendothelial surface. In animals given 50–100 ng/kg/min PGI₂, a similar layer of adherent platelets making intimate contact with the damaged surface was seen. In those animals receiving 850 ng/kg/min PGI₂, the subendothelial surface was devoid of adherent platelets. The subendothelial surface in these animals appeared normal and, at high magnification, showed the microfibrils characteristically seen in vascular subendothelium.

Quantitative morphometric analysis of the effect of PGI₂ on platelet coverage of the balloon-deendothelialized rabbit aortic surface is summarized in Fig. 4. Thirty minutes after injury, 87% of the injured aortic surface was covered by platelets in animals perfused only with Tris-buffer. Platelets covered 70% of the aortic surface of animals given 50–100 ng/kg/min PGI₂. In contrast, only 14% of the injured aortic surface of animals given 650–850 ng/kg/min PGI₂.
was covered by platelets. When these results are compared to the corresponding aggregation patterns of PRP obtained from each animal (Fig. 4) prior to balloon injury, it can be seen that inhibition of in vitro ADP- and collagen-induced aggregation correlates with the decrease in platelet surface coverage of the damaged vascular surface. The effect of infusing 850 ng/kg/min PGI2 on the attachment of 3HCr-labeled platelets to the balloon-deendothelialized aorta paralleled the morphological studies. There was an average of $1.69 \pm 0.45 \times 10^6$ platelets/sq cm of aorta in animals given PGI2, a 63% reduction from the number found attached to the surface of untreated balloon-injured animals.

Frozen sections of aortic tissue from balloon-deendothelialized animals stained for PF-4 by an indirect immunofluorescent technique are shown in Fig. 5. In animals infused with Tris-buffer alone, fluorescent material was seen throughout the intima-media with an intense line along the luminal surface, indicating attached platelets. Some fluorescence was seen in the wall of vessels taken from animals given 50–100 ng/kg/min PGI2. Although there appeared to be somewhat less fluorescent material in these vessel walls, the fluorescence of attached platelets was unchanged. In contrast, no fluorescence was seen in the media, and only a minimal amount was present along the luminal surface in animals infused with 850 ng/kg/min PGI2. These immunofluorescent studies are in keeping with the light and electron microscopic observations detailed above.

In two animals given 850 ng/kg/min PGI2 prior to and following balloon injury, the infusion was discontinued 15 min after injury and the animals sacrificed when aggregation studies had returned to normal. Electron micrographs and 1-μ sections of the aortae from these animals are indistinguishable from those of animals given no drugs and sacrificed 30 min after

---

Fig. 3. (A) An electron micrograph of an aortic segment. (B) A typical segment from a balloon-deendothelialized aorta; platelets are closely adherent to the subendothelial surface. (C) A segment from a balloon-deendothelialized animal given 50 ng/kg/min PGI2; again, platelets are seen closely adherent to the balloon-injured surface. (D) A segment from a balloon-injured animal given 850 ng/kg/min PGI2; here only 2 rounded platelets are seen over an otherwise platelet-free subendothelial surface (approximate magnification 2744x).

Fig. 4. Morphometric analysis of surface coverage by attached platelets in PGI2-treated animals compared to the simultaneous ex vivo effect of PGI2 on platelet aggregation. Surface coverage in non-PGI2-transfused animals was 87%. The aortae from animals given 50–100 ng/kg/min PGI2 were 70% covered, and those from animals given 650–850 ng/kg/min were 14% covered. The vertical bars represent the absolute range. Marked inhibition of platelet aggregation and surface coverage did not occur until high doses of PGI2 were infused.
PLATELET INHIBITION BY PGI₂

Fig. 5. Effect of PGI₂ infusion on PF-4 secretion into the aortic wall following balloon deendothelialization as detected by indirect immunofluorescence. In the upper panel, a section taken from a balloon-injured animal given only Tris-buffer is seen to be brightly fluorescent throughout the intima-media. In the middle panel is a section from an animal given 50 ng/kg/min PGI₂ in which some fluorescence is seen in the intima-media with a bright line along the luminal surface identifying attached platelets containing PF-4. The bottom panel is from an animal given 850 ng/kg/min PGI₂; in this section, no fluorescence is seen in the intima or media, and only occasional areas of fluorescence from attached platelets are seen along the luminal surface (approximate magnification 130×).

balloon injury. Quantitative analysis of platelet coverage of the vessel wall by the morphometric technique revealed that 83% of the exposed subendothelium was covered by attached platelets. This coverage is only 4% less than that observed in control animals.

DISCUSSION

Our studies demonstrate that: (1) adhesion and secretion occur shortly after endothelial cell removal; (2) total coverage of the injured surface requires only a small number of platelets that are uniformly distributed along the length of injured aortae; (3) a secreted platelet α-granule protein (PF-4) enters the vessel wall but does not increase in the surrounding plasma; and (4) PGI₂ infusion inhibits both platelet adhesion and secretion in a dose-dependent manner, which correlates with its ability to inhibit platelet aggregation in vitro.

The observation that ⁵¹Cr platelet survival remains normal in the rabbit following balloon deendothelialization was previously noted by Groves et al. In addition, they observed that the number of platelets adherent to the damaged wall decreased over the first 7 days following injury and that the exposed subendothelial surface did not appear to bind additional platelets. Our quantitative studies of platelet adhesion confirm this important observation. In fact, the number of platelets needed to completely cover the entire deendothelialized aortic surface, given the very low platelet turnover, is less than the number of platelets in 0.2 ml of rabbit blood. It is of interest that other experimental manipulations that produce in vivo vessel injury, such as homocysteine infusion, may induce continuous loss of endothelial cells and that this more sustained injury could account for the shortened platelet survival noted in these studies.

At present, it is not possible to follow the fate of secreted PDGF in vivo, and there is no direct evidence that it initiates the proliferative response of smooth muscle cells observed following an arteriointimal injury. We have previously reported that another secreted α-granule protein, PF-4, enters the vessel wall after platelets adhere to the deendothelialized aortic surface. If PF-4 is a reliable marker for the presence of PDGF, then our observations provide additional important in vivo evidence for a platelet-mediated smooth muscle response to vascular injury. However, a role for other mitogens in this process has been postulated, and extensive in vitro data exist suggesting that lipoproteins, insulin, somatomedins, and PDGF may all be important in facilitating smooth muscle cell proliferation. Indirect evidence from studies carried out in profoundly thrombocytopenic rabbits subjected to various forms of intimal injury also supports the hypothesis that platelets do play a role in smooth muscle cell proliferation in vivo.

Because of the belief that platelets initiate smooth muscle cell proliferation, various investigators have attempted to inhibit platelet adhesion to damaged vessel surfaces by the administration of aspirin, dipyridamole, or other nonsteroidal antiinflammatory agents. These studies have met with limited success. When Clowes et al. gave rats enough aspirin to markedly inhibit platelet aggregation, they could not demonstrate a decrease in adhesion to the deendothelialized vessel surface or inhibition of myointimal thickening. Others have shown that aspirin and
related compounds do not inhibit the in vitro release of α-granule proteins from rabbit platelets adhering to collagen or balloon-damaged rabbit aortic strips. 29

PGI2 is a more potent platelet inhibitor30-32 that has not yet been tested in balloon-injured animals. Current evidence suggests that PGI2 inhibits platelet aggregation and secretion by binding specific receptors and increasing intracellular levels of cyclic AMP.33,34 PGI2 is also a potent vasodilator35 and, like other prostaglandins, may block platelet production of the vasoconstrictor thromboxane A2 by its effect on cyclic AMP.36 A constant infusion of PGI2 in humans can partially inhibit in vitro platelet aggregation. However, infusion rates have never exceeded 50 ng/kg/min because of the profound vasodilatory effect of the drug.37 Various investigators have demonstrated that PGI2 can partially inhibit platelet adhesion in vitro using rabbit aortic strips exposed to flowing blood.38,39 Ubatuba et al. have investigated the in vivo action of PGI2 on aortic strips exposed to flowing blood.37,38

A constant infusion of PGI2 in humans can partially inhibit in vitro platelet aggregation. However, infusion rates have never exceeded 50 ng/kg/min because of the profound vasodilatory effect of the drug.37 Various investigators have demonstrated that PGI2 can partially inhibit platelet adhesion in vitro using rabbit aortic strips exposed to flowing blood.37,38 Ubatuba et al. have investigated the in vivo action of PGI2 on platelets following electrically induced thrombus formation in the rabbit carotid artery.39 In these studies, PGI2 infusions begun 5 min before injury could inhibit thrombus formation if the infusion rate exceeded 300 ng/kg/min.

In rabbits, it is possible to infuse PGI2 at rates as high as 1000 ng/kg/min without provoking cardiovascular collapse, and total inhibition of platelet aggregation can be attained. In our studies, total inhibition of platelet aggregation by PGI2 correlated with marked inhibition of platelet adhesion and secretion on the balloon-deendothelialized aortic surface. Inhibition could be maintained for 30 min after balloon injury but was dependent on continued infusion of PGI2. When the infusion is discontinued and platelet aggregation is allowed to return to normal, adhesion to the vessel wall is identical to control animals. This is in keeping with the observation that the deendothelialized rabbit aorta makes very little PGI2 during the first few days after injury.40 PGI2 production, in fact, does not increase until several weeks after injury and is related to the proliferation of a smooth muscle neointima.

This report provides some new insights into the role of platelets in the initial response to vascular injury since we have documented that a platelet α-granule protein actually penetrates the vessel wall and has shown that PGI2 can modify the platelet response to vascular injury and prevent the entry of platelet proteins into the vessel wall. Thus, PGI2, along with related compounds, is a pharmacologic agent that may be used to prevent myointimal proliferation after vascular injury. We also hope to have established reliable experimental techniques to evaluate the effect of other antiplatelet agents on platelet adhesion and secretion in intact experimental animals.

ACKNOWLEDGMENT

The authors wish to thank Linda Whalon for her excellent secretarial assistance.

REFERENCES

18. Groves HM, Kinlough-Rathbone RL, Richardson M, Moore...
PLATELET INHIBITION BY PGI₂


The interaction of platelets with aortic subendothelium: inhibition of adhesion and secretion by prostaglandin I2

B Adelman, MB Stemerman, D Mennell and RI Handin