Prostaglandins and the Control of Blood Flow in the Canine Myocardium

THOMAS H. HINTZE AND GABOR KALEY

SUMMARY A comprehensive study was undertaken to evaluate the effects of inhibition of prostaglandin (PG) synthesis on a variety of reactions in the coronary vascular bed of anesthetized, open-chest dogs. In 23 dogs an electromagnetic flow probe (EMFP) and hydraulic occluder were placed around either the left anterior descending or circumflex branches of the coronary artery and a needle was inserted distal to the EMFP. Injections into the coronary artery of arachidonic acid (AA), bradykinin, adenosine, angiotensin, and PGE₂ were given before and after inhibition of PG synthesis by indomethacin (IND) or meclofenamate (MF). The effects of the inhibitors on reactive hyperemia resulting from 5-, 10-, 15-, and 20-second occlusions and the dilation resulting from 90-second exposure to 8% O₂ were also examined. In each experiment, inhibition of PG synthesis was ascertained by the elimination of vasodilation to AA. After administration of IND or MF, while baseline coronary blood flow was slightly reduced, the total increment of blood flow to vasodilator agents was not significantly altered. Whereas the peak dilation and volume of reactive hyperemia were decreased, the percent flow debt repaid was unchanged and total increment of coronary flow due to hypoxia-induced vasodilation was not significantly modified. Vasoconstrictor responses to angiotensin were also unchanged. These results indicate that while inhibitors of PG synthesis increase coronary resistance, they do not adversely affect vascular responsiveness. We conclude that prostaglandins play little, if any, role in modulating coronary blood flow.

ANIMALS

Twenty-three male mongrel dogs weighing 17-27 kg were premedicated with subcutaneous morphine sulfate (3 mg/kg) and were anesthetized with an equal proportion of sodium pentobarbital (Nembutal, Abbott), 50 mg/ml, and allobarbital (Dial)-urethane (Ciba). Anesthesia was maintained with periodic injections of sodium pentobarbital, as needed. A femoral artery and vein were cannulated for infusion and blood sampling. The brachial artery was cannulated for the measurement of systemic blood pressure with a P-100A transducer (Narco Bio-Systems). Both vagi were cut to prevent reflex changes in heart rate and the dogs were intubated. An electrocardiogram (ECG) was recorded (Physiograph, Narco Bio-Systems) from needle electrodes placed subcutaneously in the forepaws and the ground on the left side of the abdomen. The intubation tube was attached to a respirator (Palmer) and the stroke volume initially was determined by weight; later, after the thorax was opened, it was adjusted to fill the lungs. A pinch clamp was placed on the outflow hose to prevent atelectasis. Blood pH and blood gases were measured from arterial samples and pump rate was adjusted to maintain PCO₂ at 40 mm Hg and PO₂ at 90 mm Hg. The temperature of the dog was maintained at 38°C by a heating pad.

SURGICAL PROCEDURES

An incision was made in the 4th intercostal space and the ribs were spread. The lungs were reflected back and
the pericardium was incised parallel to the phrenic nerve. The left atrial appendage was clamped. The left anterior descending (LAD) coronary artery was dissected free below the septal artery, and an electromagnetic flow probe (Carolina Medical Electronics) was placed on the artery. A hydraulic occluder (Rhodes Medical Instruments) was fastened on the artery proximal to the flow probe. The circumflex branch of the left coronary artery was isolated in four experiments. In most experiments a 27-gauge lymphangiographic needle was placed in the artery for injection distal to the flow probe. The flow probe was grounded to the pericardium, which was partially closed and kept moist with saline warmed to 37°C. After surgery the dog was allowed 45 minutes to recover. During this period initial blood samples were taken and the respirator was adjusted.

**EXPERIMENTAL PROTOCOLS**

Heart rate, mean arterial blood pressure, and baseline coronary flow were noted periodically before each experimental manipulation. All vasoactive substances were injected directly into the coronary artery. Injection of vasoactive substances, occlusion of coronary blood vessels, and exposure of dogs to hypoxic gas mixtures were performed before and after the injection of PG synthesis with either indomethacin (IND), 5 mg/kg (Merck Sharpe and Dohme), or meclofenamate (MF), 3.0 mg/kg (Parke Davis); thus each dog served as its own control. The inhibitors were infused into the femoral vein over 10 minutes (Harvard infusion pump).

Thirty minutes after infusion of the inhibitor the injections, occlusions, and exposures to hypoxia were repeated. At least 5 minutes were allowed after the return of coronary blood flow to baseline before the start of another experimental procedure. The order of individual injections and the sequence of paired occlusions of equal duration and of two exposures to 8% O₂ in nitrogen were randomized to prevent the conditioning of subsequent responses. Thirty minutes later the experimental protocol was repeated. At the end of the experiment an anastomosis was created between the femoral artery and vein and the flow probe was calibrated. Zero baseline was ensured during each occlusion. Adjustments due to hematocrit were unnecessary because of probe stability. The heart was removed and examined to ensure that there was no gross pathology present. The following experiments were carried out:

In five dogs reactive hyperemias resulting from LAD coronary artery occlusions for 5 seconds were studied. IND was given over 10 minutes, and 30 minutes later the reactive hyperemias were once more observed.

In one dog, reactive hyperemias and flow changes resulting from 90-second exposure to the hypoxic mixture were studied in the vascular bed of the LAD coronary artery. These procedures were repeated after IND administration.

In all of the following experiments blockade of PG synthesis was verified by the elimination of the increase in blood flow induced by the injection of 600 μg of arachidonic acid (AA) (Nucheck), the precursor of PGE₂. Injections of the following vasoactive compounds also were made before and after IND or MF: 0.1 μg of bradykinin (Sandoz); 1 μg of PGE₂, 1 μg PGF₆₂α (Upjohn); 1 μg of angiotensin II (Hypertensin, Ciba) and 0.5 μmol of adenosine (Sigma). These drugs were given in 0.8 ml and flushed twice with 0.3 ml of saline.

In seven dogs flow changes in the LAD coronary artery to reactive hyperemias resulting from 5-second occlusions, exposure to hypoxia and injections of vasoactive compounds were studied before and after IND. In one of these dogs 10% of the systemic dose of IND was given directly into the LAD coronary artery.

In six dogs LAD coronary artery occlusions of 5, 10, 15, and 20 seconds and injections of vasoactive drugs were made before and after IND infusion.

In four dogs left circumflex coronary artery occlusions of 10, 15 and 20 seconds and injections of vasoactive agents into the same blood vessel were made. In these dogs inhibition of PG synthesis was induced with MF.

Because there were no significant differences between the effects of IND and MF, the data obtained by the use of these agents have been pooled. Also, no distinction is made in this report between the LAD and circumflex coronary arteries, because their responses were quite similar.

**DRUGS**

IND in a concentration of 5 mg/ml was prepared in saline and sodium bicarbonate, and the pH was adjusted to 8 by the addition of 1 N HCl. MF was dissolved in 1 ml of hot NaOH, the volume was adjusted to 3 mg/ml, and the pH was titrated to 9. Vials containing preweighed amounts of AA were stirred with sodium carbonate overnight, under nitrogen, in the dark. A sample was taken the next day, diluted with saline, and used immediately. All other drugs were made up in saline and kept at −4°C until use.

**ANALYSIS OF DATA AND STATISTICS**

Peak responses in coronary blood flow were read off the channel that recorded mean blood flow. The "volume" of a response was calculated as the area under the mean flow curve either above or below the baseline. This was ascertained by cutting out and weighing the chart paper. Percent flow debt was calculated as: (volume of hyperemia/volume of the occlusion) × 100. Since the differences among groups of dogs for procedures common to them were not significant, all the results for a single procedure were pooled and evaluated by the two-tailed Student's t-test for paired values. The results are reported as the mean ± SEM before and after PG inhibition, together with the paired P values. For regression analysis the method of least squares was used and the significance of r values was also computed.

**Results**

**EFFECTS OF INHIBITORS OF PG SYNTHESIS ON BLOOD PRESSURE, HEART RATE, AND CORONARY BLOOD FLOW**

In each of 23 dogs the cardiovascular parameters reported in Table 1 are the average of at least three determi-
TABLE 1 Effects of Inhibitors of Prostaglandin (PG) Synthesis on Blood Pressure, Heart Rate, and Coronary Blood Flow

<table>
<thead>
<tr>
<th>Before PG inhibition</th>
<th>After PG inhibition</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>111.7 ± 2.9</td>
<td>114.6 ± 2.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>171.7 ± 3.5</td>
<td>167.4 ± 3.4</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>28.4 ± 1.8</td>
<td>24.2 ± 1.8</td>
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Results are expressed as mean ± SE; n = number of experiments.

Effects of Inhibitors of PG Synthesis on the Responses of the Coronary Circulation to Vasoactive Agents

AA, the precursor of PGE₂ and PGF₂α, the most commonly found, naturally occurring prostaglandins, produced a marked increase in blood flow in the coronary artery which was in most instances totally abolished by the administration of PG synthesis inhibitors. IND and MF are thought to interfere with the conversion of AA to PGG₂, an endoperoxide intermediate in PG biosynthesis. The inhibition of the vascular effects of AA was used as an indication of the effectiveness of PG inhibition. Figure 1 shows a retraction of an actual record of mean coronary blood flow in a dog in which the response to AA was abolished completely by IND treatment. In 16 dogs, both the peak increase and the volume of the increase in coronary blood flow were similarly affected by PG inhibitors up to a period of 4 hours (Fig. 2). In one experiment, in which 10% of the systemic dose of IND was injected directly into the coronary circulation, the complete inhibition of the response to AA lasted only 90 minutes.

To ascertain that there was no substantive decrease in vascular responsiveness to prostaglandins during the progression of each experiment, PGE₂ was administered before and after blockade of PG synthesis. Figure 1 depicts the responses of the coronary vascular bed to PGE₂ at various times during the study of a single dog. Cumulative data obtained from 16 separate experiments demonstrated that after blockade the peak increase in flow was less but that the volume of the response to PGE₂ was not significantly altered (Fig. 2). The fact that there was a positive correlation between baseline coronary flow and peak responses to PGE₂ (Fig. 3) indicates that the reduction in these responses was not necessarily due to a change in responsiveness to PGE₂ per se but rather to a fall in baseline flow brought about by the administration of the inhibitors.

Interestingly, intracoronary injection of PGF₂α (four experiments) in doses of up to 40 μg produced no observable change in coronary blood flow.

The increase in coronary blood flow resulting from in-
Regression analysis of the effects of baseline flow changes on peak responses to prostaglandin E₂.

Injection of bradykinin, an agent which according to some authors not only releases prostaglandins but whose vascular action may be dependent on the release of these agents, was unaffected by inhibition of PG synthesis. An individual record of mean coronary blood flow changes (Fig. 4) shows that there was no decrease in the response to bradykinin after IND. In Figure 2 the results of 14 experiments are shown. Neither the peak nor the volume of the responses was significantly affected when release of prostaglandins was inhibited.

Angiotensin II, an agent that has been shown to release prostaglandins in a variety of tissues, was the only substance examined that causes an increase in coronary resistance. Figure 4 depicts the changes in coronary blood flow resulting from injection of angiotensin in one experiment. The data obtained from six experiments indicate that no significant changes occurred in the volume of the blood flow reduction after the administration of IND or MF (Fig. 2). The peak decrease in blood flow is not reported, because angiotensin at the dose levels used caused complete cessation of coronary blood flow. The period of ischemia that followed each administration of angiotensin did not result in a hyperemic response.

Adenosine, thought to be an important mediator of the moment-to-moment regulation of myocardial blood flow, caused a marked vasodilation in the coronary vascular bed which, however, did not seem to be affected by IND. Experimental results obtained in seven dogs have shown no significant change in the increase in peak and volume flows induced by 0.5 μmol of adenosine which could be ascribed to PG inhibition (Fig. 2).

EFFECTS OF INHIBITORS OF PG SYNTHESIS ON REACTIVE HYPEREMIA

Figure 5 shows reactive hyperemias resulting from 5-second occlusions of the LAD coronary artery before and after IND in a single dog. The percent flow debt repaid does not seem to be altered significantly throughout the experiment, up to 120 minutes after IND administration. Increases in coronary blood flow due to occlusions 10, 15, and 20 seconds in duration performed in a single dog are depicted in Figure 6. MF did not seem to reduce significantly the reactive hyperemias in this dog as measured by the percent flow debt repaid. A compilation of the data for all the reactive hyperemias of the same duration is shown in Figure 7. The results of these experiments indicate that inhibition of PG synthesis has no significant effect on the percent flow debt repaid following occlusions of 5, 15, and 20 seconds. There was a reduction in the percent flow debt repaid after the 10-second occlusions, a finding that can perhaps best be ascribed to two unusual experiments which might have influenced our data and which we do not

![Figure 3](image-url)

**FIGURE 3** Regression analysis of the effects of baseline flow changes on peak responses to prostaglandin E₂.

![Figure 4](image-url)

**FIGURE 4** The effects of indomethacin on coronary blood flow in response to angiotensin II (1 μg) in one dog and to bradykinin (0.1 μg) in another dog.

![Figure 5](image-url)

**FIGURE 5** The effects of indomethacin on reactive hyperemias resulting from 5-second occlusions of the left anterior descending coronary artery of a single dog.
consider of physiological significance. In these instances flow debt repaid was initially 900% (well above values normally obtained), which was reduced by IND administration to the normal value of 400%.

The changes in reactive hyperemia were expressed as percent flow debt repaid, because the peak and volume of the reactive hyperemia are dependent on baseline coronary flow. This has previously been demonstrated by other authors and is also shown for the present data. As depicted in Figure 8, there is a positive correlation between the volume of reactive hyperemic flow and baseline coronary blood flow. Thus, it is imperative that when baseline flow changes occur, as they did in the present experiments, reactive hyperemic flow changes should be evaluated by percent flow debt repaid rather than peak flow or volume flow.

**THE EFFECTS OF PG SYNTHESIS INHIBITION ON CHANGES IN CORONARY FLOW DUE TO HYPOXIA**

The record obtained for a single dog on the effects of IND on mean coronary blood changes after exposure to 90 seconds of hypoxia is depicted in Figure 9. Table 2 summarizes the data obtained for 10 dogs.

The peak increase in coronary flow due to 90-second exposure to 8% oxygen was markedly reduced after PG inhibition. This reduction in peak flow may very well be due to the decrease in baseline flow caused by the administration of PG inhibitors, similar to the data obtained with PGE2. However, the volume of the response was unaltered; consequently, the oxygen debt incurred because of hypoxia was equally repaid before and after inhibition of PG synthesis.

*Figures 6, 7, 8, 9*
Inhibition on Changes in Coronary Flow Due to Hypoxia

<table>
<thead>
<tr>
<th>Before PG inhibition</th>
<th>After PG inhibition</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Peak increase in coronary flow (ml/min)</td>
<td>41.8 ± 7.6</td>
<td>34.6 ± 5.6</td>
</tr>
<tr>
<td>Volume of response (ml)</td>
<td>23.9 ± 4.5</td>
<td>21.4 ± 3.7</td>
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Results are expressed as mean ± SE; n = number of experiments.

Discussion

In our experiments inhibitors of PG synthesis caused a reduction in coronary blood flow similar to that observed in the autoperfused dog kidney. In contrast, when there is only a minimum of surgical intervention, as in the experiments of Swain et al., in the dog kidney and Owen et al., in the dog heart, there does not seem to be any increase in vascular resistance following PG inhibition. It is then reasonable to assume that the fall in baseline coronary blood flow that we observed after IND or MF administration is dependent on the abolition of basal PG release which may in turn reflect the extent of injury to the tissue.

AA has been shown by Bergström et al. to be the fatty acid precursor of PGE2 and PGF2α. In this context, in the isolated perfused rabbit heart Needleman has found that the AA-induced PG release was eliminated by IND, as measured by bioassay. As for the mechanism of the AA-induced vasodilation that we observed and also the fall in systemic blood pressure noted by Rose et al., it is quite possible that the initial part of the response is due to the endoperoxide intermediates in the course of PGE2 synthesis, and only the latter, sustained part of the response is due to PGE2 itself.

PGF2α, generally a vasoconstrictor agent, caused no change in coronary blood flow; a further indication of the fact that the vascular response to AA in this circulatory bed is due primarily to vasodilator prostaglandins. Since in the present study there was no significant reduction in the vasodilation to PGE2 after IND or MF treatment, a change in any of the vascular responses that we studied could not have been caused by a general decrease in responsiveness of coronary blood vessels due to inhibition of PG synthesis.

Bradykinin, for some time, has been suspected as the cause of anginal pain and was recently collected from the coronary sinus effluent during ischemia. It was also found by Needleman to be a potent releaser of E prostaglandins in the isolated perfused rabbit heart, especially in the presence of a bradykinin-potentiating substance. In addition, there is evidence that in the rabbit heart, the dog kidney, and rat cremaster muscle the vasodilation induced by bradykinin is at least partially dependent on PG release. Moreover, it recently has been reported that bradykinin causes an increased synthesis of a PGE-like substance in isolated arteries and of a PGF-like material in isolated veins. Our inability to demonstrate a change in the blood flow response to bradykinin after PG blockade in the intact dog heart indicates that in this experimental model bradykinin does not release a significant amount of vasodilator prostaglandins and that prostaglandins could not mediate any part of the vasodilation observed.

Angiotensin has been shown to induce PG release in various tissues, including dog kidney and isolated rabbit heart. In these experimental models and in the cremaster muscle of the rat the evidence strongly suggests that this release buffers the vasoconstriction produced by angiotensin. A recent report by Needleman et al. indicates that in the isolated rabbit heart, after 3-4 hours of perfusion, angiotensin becomes a vasodilator, undoubtedly because of the release of large amounts of vasodilator prostaglandins. Similarly in the gravid uterus, in this instance perhaps as part of a physiological response, angiotensin causes vasodilation that can be eliminated by previous administration of IND. In our experiments, however, angiotensin consistently was a vasoconstrictor as evidenced by a fall, and in most cases a complete cessation, of coronary blood flow before and after the inhibition of PG synthesis. It is difficult to reconcile the diversity of these experimental results but we suspect that in an isolated, perfused organ the angiotensin-induced release of prostaglandins may be factitiously high. It is also puzzling that in spite of the obvious O2 debt incurred by the temporary ischemia caused by angiotensin, no compensatory increase in blood flow occurred that is comparable to the one which follows mechanical occlusion of equal duration. These results would be hard to interpret on the basis of a theory that invoked the release of a vasodilator mediator purely due to oxygen deprivation.

Adenosine has been proposed as perhaps the primary regulator of coronary blood flow. On the basis of previous studies and those of Minkes et al., the conclusion can be reached that there is no functional relationship between adenosine and PG release, since the inhibitors of PG synthesis had no effect on the adenosine-induced coronary vasodilation.

If prostaglandins are involved in the regulation of coronary blood flow that is known to be dependent on the availability of oxygen, then any oxygen debt incurred should result not only in the release of prostaglandins but also an increase in blood flow which can be directly correlated with this release. In fact, PG release, confirmed by bioassay or radioimmunoassay, has been observed due to anoxia and hypoxia in the isolated rabbit heart, and due to ischemia caused by temporary occlusion of the left main coronary artery in the perfused dog heart. In all of the above experiments, however, as pointed out specifically by Block et al., PG release is not concurrent with the vasodilation observed. In fact, an enhanced PG release occurs at a time when, due to the reinstitution of normal oxygen tension in the perfusate, coronary blood flow falls back toward normal.

Alexander et al. found that in the pump-perfused dog heart the volume of the hyperemic flow after occlusions of the left common coronary artery for 10, 15, and 20 seconds was significantly less after IND or MF. In contrast to these results, Owen et al. reported that in the intact, closed-chest dog IND had no effect on peak or volume of flow due to 5- and 15-second occlusions of the LAD.
in tissues like kidney and nonexercising skeletal muscle where, O₂ extraction is low, enough O₂ might remain in the blood during the period of ischemia to permit the PG synthesis in quantities sufficient to affect the recovery of blood flow. This, however, is most likely not the case in the myocardium, where O₂ extraction, even under basal conditions, is near maximal.

In conclusion, our experimental results are compatible with the suggestion that prostaglandins are released under various experimental procedures in the myocardium, but throw serious doubt on the hypothesis that they are mediators of local physiological adjustments of coronary blood flow.

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References

coronary artery. Our results confirm those of Owen et al., in that the percent flow debt repaired was not altered significantly by inhibitors of PG synthesis. There is no ready explanation for these contradictory findings aside from pointing out that the autoperfused heart, involving little trauma to the tissue, is a more physiological preparation than the pump-perfused one. In this connection, it is of importance that the PG content of the perfusate of an isolated spleen increases progressively throughout the duration of experiments. Furthermore, in the isolated perfused rabbit heart PG release also tends to increase with the length of the experiment, filling of the balloon, massage, fibrillation, and mechanical trauma.

In our experiments the increase in the volume of coronary blood flow during hypoxia was also not substantially altered by the inhibition of PG synthesis. Afnosso et al., on the other hand, reported that IND administration slightly reduced the peak increase in flow following similar exposures to hypoxia. However, measurement of volume-flow is a better indicator of oxygen delivery to the tissue during hypoxia than measurement of peak flow. Furthermore, others have found that in the isolated perfused heart of the rabbit the anoxia-induced fall in resistance was unchanged when PG release, as measured by bioassay, was inhibited by IND. These observations strongly suggest that prostaglandins are not involved in compensatory vasodilation due to hypoxia or ischemia of the myocardium.

In this context it is of interest that the biochemical control of PG synthesis depends largely on two factors; namely, availability of substrate (AA and other fatty acids) and the activity of the PG synthetase enzyme complex. The PG synthetase complex is tonically active in vivo and also in vivo, as shown by the immediate vasodilation due to injections of AA in our experiments. Furthermore, Samuelsson has demonstrated that molecular O₂ is necessary for the production of PG endoperoxide intermediates. Consequently, when substrate is available, following the activation of phospholipase, the presence of O₂ is the controlling factor in the production of prostaglandins. An increased availability of substrate may be the result of the dissolution of membrane phospholipids by mechanical trauma, the action of angiotensin, or the stimulation of phospholipase by bradykinin. From this it would be reasonable to postulate that in intact, nontraumatized tissues in which no substrate is extant and the level of endogenous PG synthesis is consequently low, inhibition of PG synthesis does not reduce blood flow. By the same token, the reduction in baseline flow after indomethacin, also observed in our experiments, reflects augmented PG synthesis due to increased substrate availability.

Since the delivery of O₂ to the tissue is essential for the enzymatic formation of the endoperoxides, it inhere that during sustained episodes of anoxia, hypoxia, or ischemia produced by temporary occlusion when oxygen delivery to the myocardium is limited, little or no vasoactive PG can be formed. It is evident that when O₂ tension returns to normal, prostaglandins could be produced once more. It also can be argued that in tissues like kidney and nonexercising skeletal muscle where, O₂ extraction is low, enough...
Platelet Aggregation in the Cerebral Microcirculation

Effect of Aspirin and Other Agents

WILLIAM I. ROSENBLUM AND FAROUK EL-SABBAN

SUMMARY After a certain period of time filtered ultraviolet light produces platelet aggregation in microvessels on the cerebral surface of the mouse, but only when sodium fluorescein is first injected intravascularly to provide a light-absorbing, heat-generating target. The platelet aggregates fluoresce. They occur only in the illuminated field and adhere to arteriolar and venular walls. Vasocostriction is not detected prior to or up to 30 seconds after aggregation. Electron microscopy reveals damaged endothelium and undamaged red cells, as well as aggregates consisting almost exclusively of platelets in varying stages of aggregation, pseudo-aggregates were erroneously assumed to be masses of platelets if the vessels were exposed to a mercury lamp producing fluorescent platelet aggregates which makes it easier to distinguish the true diameter of the vessel from the irregular outline of the erythrocyte (RBC) column. This “time of aggregation” is prolonged by pentobarbital as opposed to urethane anesthesia, and also is related to time elapsed after cranialotomy. We also found that aspirin and indomethacin significantly prolong time to first aggregate, but only on the arteriolar side of the circulation. This is so even though the composition of the aggregates is the same on both the arteriolar and venular sides. Heparin has no effect.

PLATELET aggregates can be produced in the microvessels on the cerebral surface by damaging these vessels mechanically or by suffusing them with ADP.6,14 Several years ago we discovered that aggregates were produced in these vessels if the vessels were exposed to a mercury lamp after intravenous injection of sodium fluorescein. The aggregates were erroneously assumed to be masses of leukocytes. After review of the literature pertaining to platelet aggregation following laser injury of microvessels6-11 we realized that our model was analogous to the latter, and that the aggregates must be composed primarily of platelets. Electron microscopy confirmed this. The fluorescein dye used in our model has the advantage of producing fluorescent platelet aggregates which makes it easier to distinguish the true diameter of the vessel from the irregular outline of the erythrocyte (RBC) column. As it insinuates itself between platelet masses.12 In the studies described below we have investigated some morphological aspects of the model, and some physiological aspects including the effects of drug pretreatment on aggregation. In so doing, we have shown an inhibitory effect of aspirin on platelet aggregation, a phenomenon that has, to our knowledge, been demonstrated only once, previously, with respect to cerebral microvessels.14

Methods

MICROSCOPE AND LIGHT

A 200-watt mercury lamp was used to induce damage and to provide light for microscopic examination of the vessels after damage. When observations with some other light source were desirable, a tungsten lamp was substi-
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