Platelet Accumulation in Regions of Low Blood Flow During the Postischemic Period

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SUMMARY Various studies indicate that after a latent interval, a progressive focal deterioration of microvascular perfusion can develop in zones of acute damage to the central nervous system (CNS). In order to obtain reliable information concerning the possibility of platelet participation in this phenomenon, platelet deposition was investigated by means of 111Indium-labeled platelets, and compared with local cerebral blood flow (CBF) and cortical sensory evoked response (CSER). Studies were performed with a model of focal ischemia in which small volumes of air were injected selectively into one internal carotid artery of dogs anesthetized with alpha chloralose throughout the experiment. The ischemic period was followed by a 10-min, 60-min or 4-hr recovery period. The main result was a prominent and diffuse accumulation of platelets in zones of low CBF in dogs subjected to 4 hr recovery.

One scheme that closely corresponds to the paradigm for blood-damaged tissue interaction is the reciprocal relationship at the blood-endothelial interface between Thromboxane A2 (TXA2) and Prostaglandin I2 (PGI2), both of which are synthesized from the cyclic endoperoxide PGH2. The enzyme prostacyclin synthetase, which converts PGH2 to PGI2, is located in blood vessel endothelium, while the enzyme thromboxane synthetase, which converts PGH2 to TXA2, is located in circulating platelets. TXA2 is a platelet aggregator and vasoconstrictor, while PGI2 is an inhibitor of platelet aggregation and a vasodilator. Under normal circumstances, the balanced interaction of these potent compounds with diametrically opposite effects at the blood-endothelial interface would theoretically preserve tissue perfusion while facilitating circulatory responses ranging from hemostasis at one extreme to hyperemia at the other. Clearly, any derangement that could shift this reciprocal relationship toward a disproportionate production of TXA2 could profoundly diminish local blood flow.

Such a scheme, which implicates platelets in the postischemic impairment of cerebral blood flow (CBF), is supported by pharmacological experiments in which prophylactic indomethacin and PGI2 prevented impairment of postischemic reflow.14, 15 Furthermore, since the von Willebrand factor activity of the F VIII/vWF molecule is required for platelet-platelet interactions,16 it is possible that the interference with reperfusion associated with F VIII/vWF might also be mediated through platelet aggregation.12 Other indirect evidence exists for participation of platelets during the recirculation period following ischemia.17, 18 But all these observations are at variance with the fact that intravascular platelet aggregates have been notably absent in several histopathologic analyses of brain subjected to reversible global ischemia.19, 20 The technical difficulty of identifying clumps of intravascular platelets under the microscope, even under conditions in which the likelihood of their presence is high,21, 22 could be responsible for the discrepancy. Dougherty et al.23 demonstrated deposition of postischemic platelets, but interpretation of their results is complicated by the 3H-serotonin label which is secreted during the platelet release reaction.

In order to obtain unequivocal evidence for platelet
accommodation in tissue, a new autoradiographic technique that allows a precise localization of $^{111}$Indium-labeled platelets in brain sections was designed. $^{111}$Indium ($^{111}$In) is a cell marker that is not released from platelets. In the present studies, local CBF, neuronal function and platelet deposition were investigated in dogs subjected to a 1-hr interval of focal cerebral ischemia, followed by a 10-min, 60-min or 4-hr recovery period.

**Material and Methods**

The general model of focal ischemia was developed in our laboratory. A 1-hr period of focal ischemia was induced in one hemisphere of a dog's brain by selectively injecting small volumes of air directly through the ipsilateral internal carotid artery. Blood circulation to the opposite hemisphere remained intact as the control. The degree of ischemia was regulated by monitoring the cortical sensory evoked response (CSER) as a quantitatively electrophysiologic index of neuronal function. The ischemic period was followed by a recovery period, at the beginning of which autologous $^{111}$Indium-labeled platelets were reinjected into the systemic circulation. A study of $^{111}$C-Iodoantipyrine CBF concluded the experiment and a double-label autoradiographic technique facilitated correlation of both cerebral blood flow and platelet deposition in any given area of the brain.

Thirty conditioned, male mongrel dogs weighing 12 ± 0.6 kg (mean ± SEM) were anesthetized by subcutaneous administration of xylazine (Rompun) 1.1 mg/kg and atropine 0.05 mg/kg, followed by an initial intravenous dose of chloralose 80 mg/kg (10 mg/ml) and incremental doses as necessary. Anesthetized animals were ventilated mechanically, monitored for arterial blood pressure, temperature and blood gases, and prepared for the recording of cortical sensory evoked response as described previously.

Baseline CSERs were recorded, and 50–100 microliters of room air were injected into the side to be injured via the catheter for the internal carotid artery, and flushed in with 500 microliters of saline. After 2 min, another CSER was recorded. If the response was suppressed, no more air was infused. If the CSER was only partially suppressed, another 50–100 microliters of air were delivered. Subsequently, the periodic re-emergence of an incipient CSER was suppressed by periodically infusing a 20–100 microliter bolus of air to reduce the $P_{r} N_{r}$ amplitude of the evoked response to 5–15% of its baseline value. This cycle of alternating emergence and ischemic suppression of the evoked response was continued for 1 hr.

The 1-hr ischemic period was followed by a 10-min, 60-min or 4-hr recovery period, during which CSER, blood gases, blood pH, blood pressure and rectal temperature were monitored. Twenty ml of $^{111}$In-labeled platelet suspension were reinjected into the systemic circulation via the femoral vein catheter at the beginning of the recovery period. The local CBF study concluded the experiment.

Autologous platelets were harvested from 100 ml of arterial blood collected at the beginning of the animal preparation; 100 ml of Ringer's lactate solution were injected intravenously immediately after blood withdrawal in order to compensate for the decrease in blood volume. Platelets were labeled with $^{111}$Indium-Oxine in plasma medium, according to a slightly modified method of Scheffel et al. A detailed description of the technique has been published. Essentially, it required: (1) preparation of platelet rich plasma (PRP) from which 4 ml of platelet concentrate were obtained; (2) incubation of the platelet concentrate with 1.5 mCi of $^{111}$Indium-Oxine (MEDI-PHYSICS Inc., Emeryville, CA); and (3) washing of the labeled platelets with Platelet-Poor Plasma (PPP), prepared by packing the red cells after collection of PRP.

Detection of $^{111}$In-labeled platelets in conjunction with $^{14}$C-Iodoantipyrine in brain tissue sections was accomplished by a double-label autoradiographic technique described previously. The method involves the immediate incubation of brain sections after selectively eluting $^{14}$C-Iodoantipyrine, by means of 100% methanol, together with delayed incubation of unwashed sections in which $^{111}$In has decayed ($^{111}$In half-life = 2.8 days).

For each dog, 18 pairs of consecutive coronal brain sections taken from three different regions (anterior, middle, posterior) of the brain were analyzed. One section of each pair was washed, stained and immediately incubated for 10 days for $^{111}$In autoradiography, while the other section was saved for delayed incubation to measure local brain blood flow autoradiographically by $^{14}$C-Iodoantipyrine, exclusive of $^{111}$In. Washing and staining were performed by sequentially dipping the sections in the following solutions:

- 10 min in 100% methanol (elution of $^{14}$C-Iodoantipyrine)
- 5 min in 100% methanol (rinse)
- 5 min in 0.1% Eosin B in methanol-water 50/50 (v/v) (stain)
- 5 min in 100% methanol (destain the gray matter)
- Dry the tissue sections at room temperature

Densitometric quantitation of $^{111}$In-autoradiographs is difficult because of the punctate distribution of the isotope and the lack of $^{111}$In standards. For this reason, brain samples were subjected to gamma scintigraphy in addition to investigating $^{111}$Indium distribution autoradiographically. Once the brain sectioning on the microtome was completed, 1-mm thick coronal samples of both control and injured hemispheres — corresponding to the anterior, middle and posterior parts of the brain — were excised, collected and placed in capped tubes. Samples were later weighed and counted for $^{111}$Indium radioactivity in a PACKARD gamma counter. When damaged areas were seen by the unaided eye, they were collected in a separate tube. Radioactive concentrations of each sample were expressed as counts/min/g of fresh tissue. In each animal, radioactivity ratios for $^{111}$In were determined for each brain region relative to the radioactivity (counts/min/g) of a blood sample collected just before the end of the experiment (tissue-to-blood ratio). This allowed us to compare the radioactivity of brain tissue from animals...
with varying blood levels of radioactivity. Previous measurements demonstrated that $^{111}$In activity in blood decreases to about 90% of the initial activity (i.e., a 10% decrease) during a 5-hr observation period.24

In order to determine whether an increase of $^{111}$In radioactivity in the injured side of the brain in some animals was due to an increase of brain vascular space (e.g., vasodilation, microhemorrhages), autologous red cells were labeled with $^{51}$Cr and re-injected with the labeled platelets at the beginning of the recovery period. Brain samples were counted later for both $^{111}$In and $^{51}$Cr radioactivity.

$^{51}$Cr-labeling of red cells was performed with packed red cells obtained after collection of the PPP. One hundred $\mu$Ci of $^{51}$Cr (New England Nuclear), supplied as $^{51}$Cr-sodium chromate in solution in isotonic saline, were added and mixed with 20 ml of packed red cells. Thirty min incubation at room temperature yielded labeling efficiencies higher than 95%. Because of such high efficiencies, $^{51}$Cr-labeled red cells were re-injected directly after they were re-diluted with 20 ml of autologous plasma saved at the beginning of the blood-cell processing.

CBF autoradiograms were quantified by a technique that required an image analyzer (Space Data Systems Inc., Goleta, CA). The neuroanatomic structures to be studied were defined. This was accomplished by analyzing a brain section that had been stained to allow precise definition of white matter. Once the picture of the stained section was digitized, the contour of the white matter was defined manually with a joystick and stored in the memory for later elimination of white matter from the CBF autoradiogram section that corresponded to the stained section. Elimination of white matter is necessary since blood flows are much lower in white matter than in gray matter.

Once superimposed directly over the digitized anatomic image from the stained section, the CBF autoradiogram was digitized. A gray level, ranging from 0–255 was measured for each pixel (unit surface) of the picture area to be analyzed. The elimination of the white matter yielded a final picture depicting gray scale densities of the gray matter of the upper cerebral cortex on which computer analysis was performed. The relationship between gray scale densities and local cerebral blood flow was such that as density increased, blood flow increased.

Computer analysis of the autoradiogram area corresponding to the uninjured cortex of the control side was performed. The gray level of the pixels belonging to the control area was analyzed, and the frequency histograms of this population was computed and displayed. From these data were determined the lower and upper 1% and 5% extreme gray levels, corresponding respectively to the lower and upper 1% and 5% extreme blood flows.

The cortex of the injured hemisphere was analyzed in like manner. As calculated and displayed for the control hemisphere, a frequency histogram of the autoradiographic densities of the injured cortex was produced. The upper and lower 1% and 5% gray level values of the control population were applied to this histogram and the percentages of pixels with a gray level exceeding the values of the defined control cortex extremes were computed and considered as percentages of the injured area in each of the following flow categories:

- very low flow (gray level below the 1% low level of the control side)
- low flow (gray level below the 5% low level of the control side)
- high flow (gray level above the 5% high level of the control side)
- very high flow (gray level above the 1% high level of the control side)

For each dog and for each part of the brain (anterior, middle and posterior), information obtained from four separate sections was pooled by computing the mean percentages of areas with very low flow, low flow, high flow and very high flow. The corresponding mean and SEM values were computed lastly for each group of dogs.

### Results

Twenty-six dogs were subjected to 1 hr focal ischemia, followed by a posts ischemic recovery of 10 min (seven dogs), 1 hr (seven dogs) or 4 hr (12 dogs). Four dogs prepared identically were not subjected to air embolization.

1. **Physiologic Parameters**

Table 1 displays mean ± SEM values for blood gases and blood pH from samples drawn initially (control samples), at the end of the ischemic period and at the conclusion of the recovery period. Blood gases and blood pH were maintained within the normal range for the dog30 by adjusting respiratory rate and volume.

<table>
<thead>
<tr>
<th>Time</th>
<th>$P_{CO_2}$ (mm Hg)</th>
<th>$P_{O_2}$ (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>35.2 ± 0.8*</td>
<td>95.5 ± 2.0</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(23)</td>
<td>(22)</td>
<td>(23)</td>
</tr>
<tr>
<td>Prior to</td>
<td>34.8 ± 0.8</td>
<td>97.8 ± 1.5</td>
<td>7.38 ± 0.01</td>
</tr>
<tr>
<td>Recovery</td>
<td>(19)</td>
<td>(19)</td>
<td>(19)</td>
</tr>
<tr>
<td>End of 10 min</td>
<td>31.8 ± 1.1</td>
<td>97.8 ± 2.9</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>Recovery</td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
</tr>
<tr>
<td>End of 1 hr</td>
<td>35.5 ± 1.6</td>
<td>95.0 ± 3.4</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>Recovery</td>
<td>(6)</td>
<td>(7)</td>
<td>(6)</td>
</tr>
<tr>
<td>End of 4 hr</td>
<td>32.8 ± 1.3</td>
<td>92.3 ± 2.2</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>Recovery</td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

† Number of animals.
of brain PCO₂ accompanying ischemia. The selective injection of air through one internal carotid artery produced no rise in blood pressure and only a slight increase in heart rate, presumably because each small and slowly infused bolus of air went exclusively to the cerebral hemispheres and spared the brain stem. This inference was supported by the ¹⁴C-iodoantipyrine autoradiographs that revealed a selective impairment of perfusion in forebrain structures.

2. CSER Responses

Cortical sensory evoked responses were evaluated throughout the experiment: every 2 min during the first 10 min of the ischemic period, every 5 min during the rest of the 60-min ischemic period and every 10 min during the recovery period. The first near-field wave of the CSER — regarded as constituting the "primary response" of sensorimotor cortex to afferent stimulation via specific pathways — was measured as described previously. The peak to peak amplitude between the first two waves (P₁ to N₁) served as the quantifiable electrophysiologic index of neuronal function. Because of the dispersion of data from animal to animal, the CSER amplitude at the sampling points was expressed as a percentage of its respective control value in each animal.

The quantity of gas required to suppress the CSER was quite variable from animal to animal. The total volume of air delivered averaged 186 ± 27 microliters (mean ± SEM, n = 26), ranging from 40–700 microliters. The magnitude and direction of CSER change during the recovery period was also very variable; the evolution of the mean CSER for the 4-hr recirculation group is presented in figure 1. When compared to the measurement performed at the end of the ischemic period, the CSER index (percent of control amplitude) improved up to the 50th minute of recirculation and deteriorated slightly thereafter. The level reached after 4 hr of recirculation is, however, not significantly different than the 1-hr level of recirculation. In fact, the animals showed various patterns of postischemic evolution of CSER that are not apparent from figure 1:

- In four dogs, no recovery at all of the CSER index was observed.
- In three dogs, the CSER index increased gradually throughout the recovery period up to 25–30% of the control level.
- In one dog, the CSER index recovered in 40 min up to 45% of the control value and remained at this level.
- In four dogs, the CSER index increased during the first hour of recirculation, reached a maximum (27 to 77% of the control level), then gradually deteriorated during the rest of the recovery period (15 to 45% of the control CSER index at the end of the experiment).

3. Cerebral Blood Flow Autoradiograms

In the 60-min recovery group, autoradiographic blood-flow mapping showed focal alterations of cerebral blood flow — presumably due to persistent or recently cleared intravascular air — that were usually limited to the superolateral cortex of the injured hemisphere. These alterations were characterized by a focal zone of low flow (one dog), foci of hyperemia (three dogs) or extreme heterogeneity with low flows and high flows juxtaposed within a single neuroanatomic area (two dogs). Figure 2a presents a typical example of such heterogeneity in blood flow. This case also illustrates the particular sensitivity of the watershed areas, (i.e., the border zones in between the distribution territories of the major cerebral arteries) to ischemia induced by small volumes of air injected directly into the internal carotid artery. Figure 4 displays the mean percentages of the cortex from the injured hemisphere with a very low flow, low flow, high flow and very high flow (from left to right for each group of bars). Data from the anterior, middle and posterior parts of the brain were obtained as described in Materials and Methods, relative to the homologous control areas, respectively.

In the 60-min recovery group, autoradiographic mapping of cerebral blood flow usually showed isolated foci of hyperemia located in the upper part of the cortex (see figure 2b for a typical example). Figure 4

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Time course of CSER change expressed as percent of control amplitude in the animals that received 60 min focal cerebral ischemia followed by a 4-hr recovery period (n = 12).
displays the percentages of abnormal low flows and high flows in the cortex of the injured hemispheres of these animals.

The 4-hr recovery group showed a pattern of altered cerebral blood flow resembling the one described for the 10-min recovery group, but with more prominent areas of low blood flow. Low blood flows at this time point would not be attributed to intravascular air. Some autoradiographs are displayed as examples in figure 3, and the percentages of the cortex from the injured hemisphere with extreme blood flow densities are displayed in figure 4.

4. Autoradiographic Detection of $^{111}$Indium-labeled Platelets

In the 10-min recovery group, it was evident that platelets accumulated and appeared as small dark spots located mainly in the vicinity of large blood vessels (see figure 2a for a typical example). This pattern of platelet disposition was generally visible throughout the injured hemisphere and was not associated specifically with areas of low blood flow.

In only one dog from the 60-min recovery group was platelet accumulation evident. No difference could be detected between the control and the injured sides on
DOUBLE-LABEL AUTORADIOGRAPHY/Obrenovitch and Hallenbeck

(a) Dog A18 Middle
(b) Dog Z54 Anterior
(c) Dog X24 Middle
(d) Dog X14 Posterior

cont. inj.

cont. inj.
the autoradiograms in the other dogs of this group. In the 4-hr recovery group, a specific pattern of platelet deposition was detected where platelets tended to concentrate in regions of low blood flow (fig. 3). A good correlation was found in this group between platelet accumulation and percent of tissue area with low blood flow (p < 0.0005).

We also performed blood flow analysis by optical densitometry, according to the method described by Sakurada et al.27 These measurements indicated that

![Figure 4](image-url)
blood flows averaged 22 ± 10 ml/100g/min (n = 15) in brain areas of the 4-hr recovery group where platelets accumulated in a specific mottled pattern. This level is slightly higher than the threshold at which the CSER is abolished: 12 ml/100g/min according to Branston et al.34 and 18 ml/100g/min according to Heiss et al.35

The deposition of platelets observed on autoradio-

![Figure 5](image)

**Figure 5.** Comparison of relative radioactivities of $^{111}$-indium, tissue activity/tissue weight

\[ \frac{\text{blood activity/blood weight}}{100} \times 100 \]

between superolateral cortex from the injured and uninjured cortex. Anterior, middle and posterior refer to the tissue block from which the sample was excised. Panel A depicts mean values for the 10-min recovery group, panel B for the 60-min recovery group and panel C for the 4-hr recovery group. Open triangles represent the SEM. Relative radioactivities for non-embolized controls are also shown.
5. Hemorrhage or an Increase in the Vascular Space as the Cause of Increased $^{111}$Indium-radioactivity

In none of the experiments in which $^{51}$Cr-labeled red cells and $^{111}$Indium-platelets were injected together were increases of $^{111}$Indium radioactivity found associated with a significant increase of $^{51}$Cr radioactivity (fig. 6). Tissue/blood $^{51}$Cr activity ratios $\times$ 100 (relative radioactivity) of injured and uninjured cortex were essentially equal at each level of brain sampled. This indicates that the increase in $^{111}$Indium radioactivity was due to platelet deposition; it was not a reflection of locally increased volume of blood in the brain.

Discussion

In the 10-min recovery group, local blood flows could either be relatively high or low. Contiguous foci of low blood flow and foci of hyperemia were often observed within the same neuroanatomic structure. Platelet deposition was demonstrable within the injured cortex of this group, particularly associated with large blood vessels, but without predilection for low blood flow areas.

Focal low blood flows at this sampling point may be due to air emboli remaining in the cerebral circulation that are associated with adherent platelets. Platelet adhesion and aggregation have been demonstrated at the air-liquid interface, together with coalescence and accretion of plasma lipids, denaturation of plasma proteins, and activation of procoagulant proteins.

Punctate autoradiographic images of labeled platelets overlying large vessels may indicate direct bubble-platelet interactions as stated above and/or platelet adhesion and aggregation to bubble-damaged intima of blood vessels. Endothelial cells can be disrupted and sloughed from the vessel wall by bubbles, which have been shown to exert unique mechanical forces at the air-liquid interface. Such areas of denuded vasculature provide a surface for platelets to adhere to basement membrane, collagen and microfibrils around elastin. Platelets that adhere initially can cause more platelets to aggregate by releasing ADP. Exfoliation of endothelial cells has been demonstrated both by electron microscopic examination of damaged blood vessels and by counting circulating endothelial cells in animals subjected to decompression sickness, a disorder associated with widespread intravascular bubbles. Some observers have not found evidence of endothelial disruption, but have instead noted an acceleration of pinocytosis after air embolism. Because the punctate autoradiographic densities that denoted platelet aggregates were not always adjacent to areas of low blood flow in the 10-min recovery group, we speculate that either some of those spots designating platelet aggregates still allowed some blood to circulate or that blood supplied through collateral channels compensated for the lack of blood flow in some of the obstructed blood vessels.

The fact that in some cases hyperemic areas appeared isolated, without any adjacent areas of low blood flow suggests that hyperemia occurred within tissue damaged by ischemia. Reactive hyperemia that occurs during or after an ischemic insult is well described, and often occurs at the periphery of regions with decreased flow, secondary to an increased H$^+$ ion concentration from lactic acid and CO$_2$. Although hyperemia observed during the ischemic period itself could arise from a collateral blood supply, it is well documented that reactive hyperemia occurs when flow returns after transient circulatory obstruction. This has been demonstrated unequivocally by sequential measurements of blood flow in very small areas of cerebral cortex by the hydrogen clearance technique.

In the 60-min recirculation group, measurement of blood flow revealed mainly foci of hyperemia; low
flow areas were observed more infrequently. These findings suggest that hyperemia is a postischemic reaction that occurs in the damaged areas themselves. As with the 10-min recovery group, more platelets were found in the injured side; however, the increase was slight, detectable only by gamma counting and significant only for the middle part of the brain. The increase might reflect platelets adhering to damaged endothelium of blood vessels.

In the 4-hr recirculation group, foci of low blood flow coincided with a specific pattern of diffuse platelet accumulation, particularly in watershed cortex; a good correlation existed between these two phenomena. These results reflect the delayed impairment of microvascular perfusion that occurs in damaged brain tissue, and indicate that platelets are associated with this phenomenon.

The answer to the following critical issue would require better resolution than the present model can provide. It is important to determine whether delayed deterioration of microcirculatory perfusion contributes to progressive cellular damage or whether, conversely, progressive cellular damage leads secondarily to microcirculatory hypoperfusion. The sequential measurements of some index of cellular health and function require better resolution than the present model can accomplish. Findings suggest that hyperemia is a postischemic reaction sufficient to damage tissue triggers a process of initial transient hyperemia, followed by progressive impairment of microvascular perfusion in which platelets participate. The biochemical mechanisms responsible for these phenomena need to be defined in detail, but experimental results and theoretical considerations suggest that the changes in flow result from a multifactorial process in which factor VIII/von Willebrand factor and the prostaglandin system participate.12, 43

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The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals;" Institute of Laboratory Animal Resources, National Research Council, DHEW Publ. No. (NIH) 78-32.

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