Fibrin Contributes to Microvascular Obstructions and Parenchymal Changes During Early Focal Cerebral Ischemia and Reperfusion

Yasushi Okada, MD; Brian R. Copeland, MD; Robert Fitridge, MD; James A. Koziol, PhD; Gregory J. del Zoppo, MD

**Background and Purpose** Ischemic cerebral injury is associated with activation of the blood coagulation cascade. To elucidate the contribution of fibrin formation to microvascular injury during focal cerebral ischemia and reperfusion, we have studied the time course and the localization of fibrin deposition in cerebral microvessels and the surrounding tissue during ischemia/reperfusion in a well-described nonhuman primate model.

**Methods** Cerebral tissues from adolescent male baboons were examined after 2-hour middle cerebral artery occlusion (n=3) and after 3 hours of middle cerebral artery occlusion and 1-hour (n=6), 4-hour (n=3), and 24-hour (n=4) reperfusion; tissues from control primates (n=3) also were examined. Fibrin deposition was detected by immunohistochemical techniques using the fibrin-specific monoclonal antibody MH-1. The number and size distribution of microvessels associated with fibrin were quantified by video-imaging microscopy.

**Results** Fibrin was associated with microvessels only in the ischemic zone where severe neuronal injury was documented, its frequency increasing with the reperfusion period (F_{1,36}=3.80, P<.05). Extravascular fibrin deposition was significantly increased by 24-hour reperfusion compared with the other subjects (P<.05). Preischemia infusion of the anti–tissue factor monoclonal antibody TF9-6B4 resulted in significant reduction of intramicrovascular fibrin (P<.038 versus no intervention) at 1-hour reperfusion but had no effect on extravascular fibrin deposition.

**Conclusions** These results suggest that microvascular fibrin deposition accumulates in a time-dependent manner during focal cerebral ischemia/reperfusion and that exposure of plasma to perivascular tissue factor is partially responsible for occlusion formation. During ischemia the large plasma protein fibrinogen extravasates and interacts with parenchymal tissue factor, forming significant extravascular fibrin by 24 hours of reperfusion. (Stroke. 1994;25:1847-1854.)

**Key Words** cerebral ischemia • reperfusion • fibrin • microvascular injury • immunohistochemistry

In the brain, experimental occlusion of the middle cerebral artery (MCA) is associated with a time-dependent series of events affecting both the microvasculature and the surrounding parenchyma. 1-3 The intramicrovascular occlusive events that occur during reperfusion after global ischemia 4 and after focal cerebral ischemia 5-7 are of interest as they may relate to the nature and extent of the parenchymal injury. Recent work has suggested indirectly that, in addition to cellular elements, fibrin formation in situ may play a role in microvascular obstructions during focal ischemia and reperfusion. 5,8 Fibrin formation, which has received very little attention in this setting, may affect microvascular flow and may give clues to the generation of hemorrhage during ischemic injury.

Generation of fibrin from fibrinogen by thrombin occurs as plasma is exposed to activated platelets; vascular tissue factor (TF), 7,10 or other stimuli. 11 Thrombin may be formed when platelets are activated by platelet-activating factor or when endothelial injury exposes underlying collagen, 9 or when polymorphonuclear (PMN) leukocytes become activated by any of a number of stimuli. 12 The possibility that fibrin may cause cerebral microvascular perfusion defects was suggested by the significant reduction in postreperfusion occlusions after preischemia exposure to heparin and ticlopidine in a nonhuman primate model of MCA occlusion/reperfusion. 9 Those observations confirmed a similar effect on microvascular patency when heparin was used in a macaque model of 4-hour MCA occlusion/reperfusion. 5 The potential contribution of TF activity to microvascular occlusion during focal cerebral ischemia/reperfusion was recently suggested by the observation that an anti-TF monoclonal antibody (MoAb), TF9-6B4, 13 increased microvascular patency in the ischemia/reperfusion zone when infused before MCA occlusion. 7 In a limited study using the same model, fibrin was found to be associated with PMN leukocytes and degranulated platelets in the obstructed capillaries. 6
In the present study, fibrin deposition in cerebral microvessels and the surrounding parenchyma of the basal ganglia during MCA occlusion/reperfusion was visualized directly using a murine anti-human fibrin-specific MoAb that recognizes both human and baboon fibrin but not fibrinogen. To further test the hypothesis that exposure of TF activity during ischemia results in intravascular fibrin formation, the effect of TF9-6B4 on microvascular and parenchymal fibrin deposition was directly examined.

Materials and Methods

Sixteen adolescent male baboons (Papio anubis/cynocephalus) weighing 8.0 to 11.4 kg were used for the MCA occlusion and occlusion/reperfusion studies, and 3 separate primates weighing 9.2 to 25.0 kg served as controls. Tissues from 15 of the animals (MCA occlusion, MCA occlusion/reperfusion, and controls) were from subjects reported previously. No animal had evidence of dis ease during the 7-day quarantine period before entry into this study. The procedures used throughout this study were approved by the institutional animal research committee and were performed in accordance with standards published by the National Research Council (The Guide for the Care and Use of Laboratory Animals), the National Institutes of Health, and the US Department of Agriculture Animal Welfare Act. In compliance with these standards, every effort was made to ensure that the subjects were free of pain or discomfort. The principal investigator, veterinarian, and primate handling staff were present for all procedures.

Preparation of the nonhuman primate model of MCA occlusion and MCA occlusion/reperfusion has been described in detail elsewhere. All animals were allowed a 7-day interval after the surgical implantation procedure before entry into the experimental protocol. The subjects were all clinically free of infection or apparent inflammation and had normal neurological function. In the time-course study, 3 animals underwent MCA occlusion for 2 hours, while 10 animals underwent MCA occlusion for 3 hours and subsequent reperfusion for 1 hour (n=3), 4 hours (n=3), or 24 hours (n=4). A separate group of 3 animals did not undergo any model preparation procedure and served as a control group. In addition, a cohort of 3 animals received 10 mg/kg of TF9-6B4 by bolus intravenous infusion 10 minutes before MCA occlusion and subsequent reperfusion of 1 hour, as in a previous study. The experimental paradigm previously reported for this awake model was followed here exactly.

Each experiment was terminated by transcardiac pressure perfusion with isosmotic perfusion flush solution during reperfusion under Pentothal sodium anesthesia (15-mg/kg infusion and mechanical ventilation. The chilled perfusion flush solution and the method of perfusion of the cranial structures have been described elsewhere. Perfusion pressures were 180 to 210 mm Hg with flow of 700 to 800 mL/min for 4 minutes. The brain was then excised en bloc from the cranium and immersed in ice-cold tissue blocks (1.0x0.4x0.2 to 0.5 cm) from symmetrically located sites of the left and right basal ganglia and the temporal and parietal cortices were embedded in Tissue-Tek OCT compound (Miles Inc), frozen in 2-methylbutane/dry ice, and stored at −70°C until sectioning.

Well-characterized murine MoAbs were used for the immunohistochemical studies. The MoAb CLB HEC-75 against the ubiquitous endothelial cell adhesion receptor E-selectin was provided by J. van Mourik (Central Laboratory van de Bloedtransfusiedienst, Amsterdam, Netherlands) or was obtained commercially (DAKO-C31, JC/70, DAKO Corporation). The murine anti-human fibrin MoAb MB-1 was the kind gift of American Biogenetic Sciences. This antibody specifically recognizes antigenic epitopes unique to the intact human fibrin polymeric structure, which is not found on fibrinogen, fibrin monomer, or fibrin degradation products. The specificity of the antibody to baboon fibrin was additionally confirmed by an enzyme-linked immunosorbent assay (ELISA) procedure, which identifies freely soluble fibrin. In this assay, soluble fibrin polymer is produced in vitro from citrated plasma by the addition of thrombin (0.025 NIH U/mL). MB-1 is used both as the capture and as the signal antibody conjugated to horseshad peroxidase for the colorimetric determination of soluble fibrin polymer (Fig 1). Previous studies using another detection system indicated a fourfold lower avidity of MB-1 to baboon fibrin than human fibrin. Purification of the murine anti-human TF MoAb TF9-6B4 from cell culture for infusion has been described previously. The TF9-6B4 product (R.W. Johnson Pharmaceutical Research Institute, La Jolla, Calif) was more than 90% pure by sodium dodecyl sulfate–polyacylamide gel electrophoresis analysis and had endotoxin levels <2 endotoxin U/mL by standard limulus amebocyte lysate chromogenic assay (Whittaker).

Consecutive 10-μm cryostat sections from matched regions of the post-ischemia/reperfusion (right) and normal non-ischemia/reperfusion (left) basal ganglia separate from those previously prepared were prepared for immunohistochemistry. Two separate blocks from each region per subject were chosen to provide at least six blocks per time point. Sections were fixed with methanol for 3 minutes at 4°C, immersed in 100 mmol/L glycine in phosphate-buffered saline (PBS; 100 mmol/L Na2HPO4/NaH2PO4 and 140 mmol/L NaCl adjusted to pH 7.4) for 10 minutes, rinsed with PBS wash solution, and subsequently incubated with Biotin20 to reduce nonspecific binding. For the MCA occlusion and MCA occlusion/reperfusion specimens, 50 μL of the primary antibody was incubated on each section for 120 minutes, washed, and then incubated with biotinylated horse anti-mouse immunoglobulin G (IgG; 1:400 in reagent diluent; Vector Laboratories) at 37°C for 30 minutes. Subsequent development of the peroxidase signal with the chromogen substrate 3-amino-9-ethyl carbazole (AEC Kit, Biomedica Corporation) was as described. Specimens from subjects that received the murine MoAb TF9-6B4 were stained separately using biotin-labeled purified MB-1 as the primary antibody to avoid the interaction of the horse anti-mouse IgG with TF9-6B4 in the tissues. Parallel experiments with selected specimens at 1-hour reperfusion using biotinylated MB-1 gave identical results with MB-1 as the primary antibody. All sections were counterstained with Mayer's hematoxylin and eosin.
er's hematoxylin (Biomedica Corporation) for 1 minute, blued
in saturated sodium bicarbonate solution, and mounted. Con-
trols routinely performed for each experiment included (1)
deletion of the primary antibody, (2) deletion of the secondary
antibody, and (3) the use of TIB115, a murine MoAb against
the SV40 large T viral antibody, as an irrelevant primary
antibody.

To further identify fibrin deposition in parenchymal tissues,
adjacent sections were stained using the primary MoAb MH-1
with fluorescein isothiocyanate-conjugated anti-mouse IgG
(Vector Laboratories).

The absolute number and minimum transverse diameters of
manually identified microvessels containing CD31 or fibrin
antigen from the basal ganglia of post-ischemia/reperfusion
and nonischemic territories were determined with the comput-
erized video-imaging system described previously.6 Minimum
transverse diameters of peroxidase-stained vascular structures
from nonoverlapping images (×400) in a standard 1000-field
matrix (66.4 mm²) were computed from each section with a
linear measurement program. The number of vessels of diam-
eter less than 100 μm stained by the MoAb CLB-HEC-75 was
regarded as the total number of microvessels per field.1,17,21

Off-line analysis of the microvascular distribution was per-
formed with resident statistical programs. Fibrin deposition is
presented as the fraction of peroxidase-stained vessels with
fibrin to those displaying CD31, and configuration 3 (fibrin lattices in the extravascular and/or
parenchymal tissues only) (Fig 2). The presence of ischemic
injury, indicated by the relative degree of neuron damage, was
assessed by using a modification of the method of Eke et al22
as described previously. The 1000-field matrix was scanned
for evidence of neuron damage, and this was correlated with
fibrin deposition. Areas where type IV neuron silhouettes
were found corresponded to variable degrees of visible tissue
disturbance; tissue peripheral to those regions had some type
II or III neuron damage.

All values are expressed as the mean or as the mean±SD.
Data from at least six matched blocks per time point were
analyzed. Statistical comparisons among the different time
points were performed with ANOVA followed by Tukey's
multiple comparison method. Data from the cohort that
received TP9-6B4 was compared with the 1-hour reperfusion
MCA occlusion/reperfusion data (no intervention) using Stu-
dent's t test, one-tailed. Significance was set at P<.05 for all
comparisons.

Results

Hemiparesis and/or unresponsiveness to tactile and
visual stimuli contralateral to the MCA occlusion ap-
ppeared within 5 to 10 minutes after MCA compression
in each subject. A significant and persistent reduction in
neurological score from 100 to 41.1±14.7 at 1 hour
after MCA occlusion was observed in both MCA-
occlusion and MCA-occlusion/reperfusion cohorts.
Baseline blood cell count data were not different among
cohorts or from those previously reported.
There was no significant difference in the frequency of reperfusion cohorts.

Intravascular fibrin (•, configuration 1) among the ischemia/reperfusion, 4-hour reperfusion (all P<.05; see also text and isons:

The frequency of total fibrin (•) and extravascular fibrin (•, configurations 2 and 3; A, configuration 3) increased during greater than in the control cohort (C; P<.05) (see Tables 1 and ision and 1-, 4-, and 24-hour reperfusion) was significantly among the time points of reperfusion when configuration versus control, 2-hour MCA occlusion, and 1-hour reperfusion, 10.1±10.8% at 4-hour reperfusion, and 14.3±6.6% at 24-hour reperfusion (F^2=3.80, P<.05) (Table 1, Fig 3). The mean frequency of microvessels with fibrin in configuration 1 ranged from 2.9% to 4.8% and was highest at 1-hour MCA occlusion/reperfusion.

There was no significant difference in the mean frequency of microvessel-associated fibrin (4.5% to 8.3%) among the time points of reperfusion when configurations 1 and 2 were considered together. Parenchymal (extravascular) fibrin deposition in the ischemic basal ganglia increased successively after 1-hour reperfusion and was most prominent at 24-hour MCA occlusion/reperfusion (P<.05 for 24-hour MCA occlusion/reperfusion versus control, 2-hour MCA occlusion, and 1-hour and 4-hour MCA occlusion/reperfusion) (Table 2, Fig 3). Taken together the frequency of extravascular fibrin, whether in the perivascular space or the parenchyma, was also significantly increased at 24-hour MCA occlusion/reperfusion (configurations 2+3=11.0±5.2%) compared with that of the other subjects (P<.05) (Fig 3).

Fibrin was seen in microvessels of which 9.4% were 4.0 to 7.5 μm in diameter (capillaries), 86.2% were 7.5 to 30.0 μm in diameter, 4.0% were 30.0 to 50.0 μm in diameter, and 0.4% were 50.0 to 100.0 μm in diameter, indicating that fibrin was most commonly associated with microvessels in the range of 7.5- to 30.0-μm diameter. Microvessel-associated fibrin, whether intravascular, extravascular, or both, was confined to regions with type IV neuronal injury (98% type IV).

Infusion of the anti-TF MoAb TF9-6B4 just before MCA occlusion targeted perimicrovascular TF in the region of ischemic injury (Fig 4). TF9-6B4 significantly reduced fibrin deposition in the intravascular compartment (configuration 1) compared with the control co-


Table 2. Localization of Microvessel-Associated Fibrin (Fibrin/CD31)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Duration, h</th>
<th>Non-I/R</th>
<th>Config 1</th>
<th>Config 2</th>
<th>Config 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>0.000±0.000</td>
<td>0.000±0.000</td>
<td>0.000±0.000</td>
<td>0.000±0.000</td>
</tr>
<tr>
<td>MCA:O</td>
<td>2</td>
<td>0.000±0.000</td>
<td>0.029±0.025</td>
<td>0.016±0.015</td>
<td>0.003±0.002</td>
</tr>
<tr>
<td>MCA:O/R</td>
<td>1</td>
<td>0.000±0.000</td>
<td>0.048±0.047</td>
<td>0.012±0.016</td>
<td>0.005±0.006</td>
</tr>
<tr>
<td>MCA:O/R</td>
<td>4</td>
<td>0.000±0.000</td>
<td>0.038±0.051</td>
<td>0.039±0.044</td>
<td>0.024±0.025</td>
</tr>
<tr>
<td>MCA:O/R</td>
<td>24</td>
<td>0.000±0.000</td>
<td>0.033±0.020</td>
<td>0.050±0.030*</td>
<td>0.060±0.032†</td>
</tr>
<tr>
<td>+ Anti-TF</td>
<td>1</td>
<td>0.000±0.000</td>
<td>0.008±0.015†</td>
<td>0.009±0.018</td>
<td>0.003±0.005</td>
</tr>
</tbody>
</table>

Non-I/R indicates nonischemic zone; Post-I/R, ischemia/reperfusion zone; MCA:O, middle cerebral artery occlusion only; MCA:O/R, 3-hour middle cerebral artery occlusion with indicated periods of reperfusion; Anti-TF, anti-tissue factor antibody, TF9-6B4; and Config, configurations of fibrin deposition: 1, intravascular stain; 2, intravascular and extravascular stain; 3, extravascular stain.

*P<.05 vs control.
†P<.05 vs control, 2-hour MCA:O, 1-hour MCA:O/R, and 4-hour MCA:O/R.

The fate of fibrinogen in situ (through its conversion to fibrin) during focal cerebral ischemia and reperfusion has not been rigorously examined, although several experimental studies have suggested a role of thrombin activation in focal cerebral ischemia.5,6,8 This in situ fibrin localization study follows from an initial morphological survey of microvascular occlusion formation after MCA occlusion/reperfusion in the primate.1-6 (See also Fig 5 in del Zoppo et al.) Fibrin was only detected in microvessels of the ischemic basal ganglia where it accumulated in a time-dependent manner, being most prominent at 24 hours of reperfusion. The majority (approximately 86%) of microvessels containing fibrin were 7.5 to 30.0 μm in diameter, consistent with the known association of TF with microvessels greater than 10 μm in diameter in primate brain.7,21 It is evident from the anti-TF infusion experiments that perivascular TF is at least partially responsible for intravascular fibrin formation in this setting. This is supported by the additional finding here that increased permeability of microvessels during ischemia/reperfusion allowed binding of TF9-6B4 to perivascular TF (Fig 4). Unfortunately, because of the murine origin of both MH-1 and TF9-6B4, colocalization of fibrin and TF was not possible.

The generation of fibrin within the microvascular compartment during MCA occlusion and occlusion/reperfusion and the potential involvement of TF have important implications.6-7 For instance, intravascular fibrin formation may also be affected by the interaction of platelets with PMN leukocytes, by platelet activation, and/or by the activation of monocytes and vascular macrophages. P-selectin has recently been shown to mediate the interaction of granulocytes with platelets and with stimulated endothelium in the ischemic cerebral tissue1 and to separately promote granulocyte/endothelium-mediated fibrin deposition.4 For instance, intravascular fibrin formation may also be affected by the interaction of platelets with PMN leukocytes, by platelet activation, and/or by the activation of monocytes and vascular macrophages. P-selectin has recently been shown to mediate the interaction of granulocytes with platelets and with stimulated endothelium in the ischemic cerebral tissue1 and to separately promote granulocyte/endothelium-mediated fibrin deposition.4 The fraction of microvessels containing fibrin in this setting complements the previous findings of microvascular endothelial cell expression of P-selectin and intracellular adhesion molecule-1 (ICAM-1) in early post-ischemia/reperfusion.1 Thrombin promotes ICAM-1–dependent granulocyte adhesion to endothelial cells, suggesting that upregulation of ICAM-1 activity may also involve fibrin formation in and around the microvessels.23 A relation between endothelial cell P-selectin expression and fibrin formation, potentially through thrombin gen-

Fig 4. Photomicrograph of localization of the murine anti-human tissue factor antibody TF9-6B4 on the abluminal side of a microvessel 26.8 μm in diameter signaled by biotin-labeled antimurine immunoglobulin. This demonstrates microvascular permeability to TF9-6B4 at 1 hour of reperfusion after 3 hours of middle cerebral artery occlusion and its binding to perivascular tissue factor.

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meability alterations as suggested by experiments with MCA occlusion in cats. However, it cannot be excluded that increased vascular permeability may contribute to extravascular ischemia/reperfusion, fibrinogen, clotting factors, platelets, endothelial cell adhesion receptors, and leukocytes has not been established.

The finding of TF9-6B4 on the abluminal portion of microvessels in the ischemic region, together with the appearance of fibrin in the striatal parenchyma, underscores the permeability of the blood-brain barrier to IgGs. Heretofore, albumin (66 kD), perhaps for practical reasons, has been the largest molecule described in the edema associated with focal cerebral ischemia. Fibrinogen was detected as an extravasated protein in a rodent model of cerebral ischemia and reperfusion. The precise intravascular relation of fibrin, platelets, endothelial cell adhesion receptors, and leukocytes has not been established.

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The finding of fibrin in the ischemic parenchymal tissue at longer reperfusion periods has several implications. Perivascular fibrin deposition presumes an increased permeability in endothelial cell vascular permeability and exposure of perivascular TF to the intravascular compartment. Increased vascular permeability may contribute to extravascular fibrin deposition in many tissues. Hence, with the elaboration of cytotoxic vasogenic edema during focal cerebral ischemia/reperfusion, fibrinogen, clotting factors, and other plasma proteins extravasate, interact with parenchymal TF, and generate fibrin in those tissues. Such events closely resemble those described for wound healing. The distribution of fibrin only in those regions with type IV neuronal injury most probably reflects the distribution of reduced regional cerebral blood flow and permeability alterations as suggested by experiments with MCA occlusion in cats. However, it cannot be excluded that fibrin deposition occurred as a secondary consequence of parenchymal damage. These experiments imply that extended reperfusion might therefore promote extravascular fibrin deposition. How the duration of ischemia might alter the ultimate fibrin deposition is not known. One issue raised in this model is the variation in fibrin deposition among separate subjects in the early reperfusion cohorts (Table 1). These variations were associated with differences in ischemic damage in those tissues. Thus, the effect of the anti-TF MoAb on intravascular fibrin deposition at longer reperfusion periods, as well as shorter ischemic periods, may be of interest.

In another example of experimental cerebral ischemia, fibrin deposits were recognized in the ischemic brain tissue of those animals who died from fatal cerebral ischemia and vasospasm. But in a rodent model of disseminated intravascular coagulation induced by continuous intravenous infusion of Escherichia coli endotoxin, fibrin deposition in cerebral vessels was uncommon. Fibrin deposits have also been seen in human acute renal failure of ischemic origin, perhaps a parallel situation. Fibrin deposition, mainly intravascular (Bowman's space) and tubular (urinary space), has been demonstrated in a rodent acute renal failure model after renal artery occlusion/reperfusion and could be prevented by heparin. Heparin or warfarin pretreatment significantly decreased renal fibrinogen and albumin content, and arvin improved glomerular filtration rate in separate studies with rat renal ischemia models.

Although noncapillary microvessels were involved in these studies, it cannot be excluded that in some instances severe trauma to large vessels occurred by direct ischemic injury with consequent local leakage. This may offer one manifestation of ischemia-related hemorrhage. Among the various phenomena associated with microvascular perfusion disturbances in the brain after ischemia/reperfusion, fibrin deposition might be more sensitive to treatment than other causes of microvascular occlusion. In addition to treatment with anti-TF strategies, early use of antithrombins (e.g., hirudin), platelet fibrinogen receptor (the α2β3-integrin, GPIIb/IIIa) antagonists, or fibrinolytic agents may alter fibrin formation in the cerebral microvasculature during or after focal cerebral ischemia and reperfusion. Determining whether and how such strategies may also affect extravascular fibrin formation should help elucidate the origins of hemorrhagic transformation.

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References
Fibrin deposition is an integral part of the pathobiology of cerebral ischemia. Prior work from this laboratory has shown that fibrin deposition occurs as a consequence of the reperfusion of ischemic tissue. This study is an extension of previous work from this laboratory on the microvascular consequences of transient focal ischemia. Prior investigations have documented the postischemic accumulation of polymorphonuclear leukocytes as well as the endothelial expression of P-selectin and intercellular adhesion molecule-1 (ICAM-1) in baboons using a fibrin-specific monoclonal antibody. Fibrin formation is increased with extended reperfusion periods and was restricted to damaged parenchymal areas. In addition, pretreatment with an anti-tissue factor monoclonal antibody reduced intravascular fibrin deposition.

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