Digital angiographic quantification of blood flow dynamics in embolic stroke treated with tissue-type plasminogen activator

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Computer analysis of digital subtraction angiography (DSA) was utilized to quantify the effectiveness of tissue-type plasminogen activator (TPA) in a rabbit cerebroembolic stroke model. Fourteen animals underwent cannulation of the facial artery and a preembolus angiogram. Autologous blood clots were then injected, and occlusion of the internal carotid artery at the circle of Willis was documented with repeat angiogram. The experimental group received a 1-mg/kg intravenous infusion of TPA via a femoral catheter for 90 minutes. A control group received an equivalent volume of saline. Follow-up angiograms were performed every 15 minutes. The TPA-treated animals showed progressive improvement in flow through previously occluded vessels. Time-density curves of the contrast material over the middle cerebral artery trunk and brain parenchyma were generated. The best integrated curves for the two groups were compared at 30 minutes after occlusion and 90 minutes after treatment. Animals were then observed for 24 hours and their neurological status was documented. Premortem infusion of either Evans blue dye or neutral red dye was performed and the integrity of the blood-brain barrier and tissue perfusion were assessed by video planometry. Significant improvements were noted by DSA, and Evans blue and neutral red dye studies in animals treated with TPA.

KEY WORDS: • blood flow dynamics • plasminogen activator • digital angiography • diagnostic imaging • rabbit

TISSUE-TYPE plasminogen activator (TPA) has been produced via recombinant deoxyribonucleic acid (DNA) techniques and is currently utilized in a cooperative human coronary thrombosis study. The preliminary results have revealed thrombolytic efficacy and minimal bleeding complications. Previous cerebral autologous blood clot models have been established in rats and dogs. Recent work in rabbits documents ischemic changes with surgical occlusion of major cerebral vessels. Zivin, et al., administered TPA to rabbits after the blind injection of 2000 to 4000 small clots, and documented a greater survival rate and decreased neurological morbidity in treated animals. Recently, Penar evaluated TPA in a rat embolic model similar to this current experimental design (unpublished data, 1986); however, he utilized only a 0.3-mg/kg dose of TPA and neglected to account for the species specificity of human TPA, which has only 10% efficacy in rats (human blood shows 95% and rabbit blood 60% efficacy). Despite these limitations he was still able to show a statistically significant decrease in volume of ischemic tissue with therapy.

This study was designed to investigate the efficacy of TPA lysis of autologous clot in the rabbit cerebral circulation. Serial digital subtraction angiography (DSA) images were used to document the time course and degree of clot breakdown and to quantify the restored flow in the middle cerebral artery (MCA) and brain parenchyma. Animals were observed for neurological deficits, and finally the blood-brain barrier integrity and cerebral perfusion were assessed by video planometric measurement of stained cerebral tissue after Evans blue or neutral red dye infusion.

Materials and Methods

Animal Preparation

This study was performed in compliance with the National Institutes of Health “Guide for the Care and Use of Laboratory Animals” and was further approved by the University of California (Davis) Animal Review Committee. In addition, constant postoperative care was maintained by the principal investigator for the duration of each experiment. Adult New Zealand White rabbits, ranging in weight from 1.8 to 2.4 kg, were...
anesthetized with 96% oxygen and 4% halothane and were then maintained on 2% halothane delivered via a mask. A midline skin incision was made on the neck extending from the thyroid cartilage to the angle of the mandible. The jugular vein was exposed and 0.5 ml of blood was drawn and placed into No. 20 Teflon tubes (inner diameter 0.034 in.) attached to 1-ml syringes which were set aside for later use as a source of clot. Surgery was continued under an operating microscope and a micropipette electrocautery was used to control bleeding. The left hyoid bone was resected to improve access to the external carotid artery. The dissection proceeded to expose the distal 2-cm segment of the common carotid artery, the origin of the internal carotid artery, the trunk of the lingual-maxillary artery complex, and the proximal 3 cm of the facial artery. The thyroid artery and all other small branches arising from the arteries described above were ligated or cauterized. A 5-0 silk ligature was placed on the facial artery, 3 cm from its origin off the common carotid artery. A second, loosely tied ligature was placed on the facial artery where it branches from the common carotid artery. A cannula was constructed from a 15-cm length of PE-50 tubing that was sleeved over a No. 23 blunt needle attached to a 1-ml syringe filled with heparinized saline. The tip of the cannula was beveled to facilitate cannulation of the facial artery. Next, 0.2 ml of 0.5% Xylocaine (lidocaine) was irrigated onto the exposed arteries and allowed to remain in contact for several minutes. A Heifetz temporary aneurysm clip was placed on the external carotid artery distal to the origin of the internal carotid artery. Thus, flow through the internal carotid artery to the brain was maintained throughout surgical manipulation. The lingual-maxillary artery complex was ligated where it branches from the external carotid artery. An arteriotomy was made in the facial artery which had no blood flow. The cannula was placed into the facial artery and passed retrograde until the tip reached the Heifetz clip on the external carotid artery. The ligature on the facial artery was snugged down and the clip was removed. The cannula was further secured in the facial artery and flushed with 0.2 ml heparinized saline. Attention was then directed toward the placement of a PE-50 cannula, attached to an infusion pump, in the left femoral vein.

Angiographic Techniques

The animal was transferred to the angiography table in a supine position, and 2% halothane ventilation was maintained by face mask. The facial artery cannula was connected to a 20-ml syringe containing an equal volume of Renografin-76 and normal saline. The syringe was placed into a Harvard infusion pump for volumecontrolled injection of contrast material during the arteriographic studies. The DSA was performed using an ADAC unit* with the small focal spot, at 60 kV, 0.8 mA, and 0.04 cc/sec of 50% contrast solution was injected for a period of 6 seconds for a total of 0.24 cc per study. A baseline study was performed to document the left hemisphere cerebrovascular anatomy in each animal.13,14 Next, the preformed autologous blood clot was extruded from the Teflon tubing and injected via the facial artery cannula into the common carotid artery proximal to the origin of the internal carotid artery. The clot then migrated spontaneously with the blood flow up the internal carotid artery (the only patent artery) to lodge at either the internal carotid artery bifurcation or the proximal anterior cerebral artery or MCA. A repeat angiogram was then performed to verify the clot position and resultant vascular occlusion. If necessary, a second clot was injected to obtain complete or nearly complete occlusion. An additional study was performed at 30 minutes after embolization to document stability of the clot and degree of obstruction prior to initiation of treatment.

The treated animals received a 1-mg/kg/hr constant infusion of TPA† into the left femoral vein cannula for 75 to 90 minutes via a Harvard pump. Control animals received an equivalent infusion of intravenous normal saline for the same time period. Angiograms were performed at 15-minute intervals up to 120 minutes after initiation of therapy. Each study was recorded on tape, and digital images (1 frame/sec) were acquired to 512 x 512 x 8-byte matrix resolution.‡ From the subtracted images, a light pen was used to select a 5 x 10-pixel (approximately 2.5 x 5-mm) region of interest (ROI) over the proximal MCA and a corresponding region of brain parenchyma devoid of vascular structures and located 3 to 5 mm directly below the MCA ROI. In addition, a background ROI outside the animal's skull was placed within the radiographic image for quantification of radiation scatter and image-intensifier glare. The tape was then replayed and the image intensities of the 50 pixels within each ROI were linearly digitized and fed to the system's host computer where the average intensity of pixels was calculated and stored. The data were then processed to produce plots of iodine concentration versus time. Correction for radiation scatter and image-intensifier glare was made by linearly subtracting the background ROI intensity from the MCA and parenchymal ROI intensity. This subtraction was performed for each individual point of the curve. The area under the curve was determined by integration of the curve from Points 1 to 12, where Point 1 represents the initial upward inflection and Point 12 the end of the washout phase.

The cannula was then removed from the facial artery, and the wounds were closed in a single layer. Anesthesia was terminated and the animal observed for the next 24 hours. Level of consciousness, response to threat,

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* Digital subtraction angiography unit manufactured by ADAC Laboratory, Milpitas, California.

† Tissue-type plasminogen activator supplied by Genentech, Inc., South San Francisco, California.

‡ Digital radiographic system, Model DPA-4100, manufactured by ADAC Laboratory, Milpitas, California.
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**FIG. 1.** Selected left internal carotid artery (IC) digital subtraction angiograms.  
*Upper Left:* Normal rabbit anatomy showing the common carotid artery (CC), the IC, the junction of the IC with the circle of Willis (IC/CW), the anterior cerebral artery (ACA), the ophthalmic artery (OA), and the middle cerebral artery (MCA).  
*Upper Right:* Image obtained 30 minutes after clot injection showing nearly complete occlusion of the IC.  
*Lower Left:* Return of the flow is seen after 90 minutes of intravenous infusion of tissue-type plasminogen activator (TPA).  
*Lower Right:* The regions of interest over the proximal MCA, underlying the parenchyma, from the background are indicated by the boxes.

and motor strength were recorded by the principal investigator and chief laboratory assistant.

**Dye Injection and Planometry**

Premortem intravenous infusion of a solution of either Evans blue dye or neutral red dye (toluylene red chloride: 3-amino-7-dimethylamino-2-methylphenazine hydrochloride) was achieved via the femoral vein catheter. The dye infusions lasted 3 to 5 minutes, followed by a fatal dose of pentobarbital. The stained brains were removed immediately from the calvaria and either deposited in a formalin solution (Evans blue-dyed specimens) or an isopentane/dry ice slurry (neutral red-dyed specimens) for 5 minutes. The neutral red-dyed specimens were stored at 0° prior to sectioning.10

The formalin-fixed Evans blue- and frozen neutral
FIG. 2. Plot of the regions of interest over the middle cerebral artery (MCA, solid line) and underlying the parenchyma (dashed line) versus time. The contrast enhancement is represented in digitalized numbers of degree of x-ray attenuation that is proportional to the amount of Renografin passing through the regions of interest at each second during the study. The temporal sequence from left to right shows baseline values and nearly complete occlusion after embolization. The curves for the areas over the MCA and under the parenchyma returned to 93.1% and 80.8% of baseline, respectively, after treatment with tissue-type plasminogen activator (TPA).

red-dyed brains were sliced in three places. Approximately 5-mm cuts were made through the posterior parietal, midparietal, and temporal tip regions. The slices were numbered and photographed under the microscope with Kodak Ektachrome 35-mm color film. The slides were then projected onto a videoplanometry unit,§ and a light pen was utilized to obtain computer-assisted measurements of abnormal areas of staining in the left hemisphere and basal ganglia. Slides of the entire slice area were also obtained and halved for calculation of area of involvement versus slice area.

Results

Selected DSA images of the left internal carotid artery revealed some anatomical variations; however, in all studies the MCA, anterior cerebral, internal carotid, ophthalmic, and common carotid arteries were identified (Fig. 1 upper left). The baseline studies showed initial filling of the common carotid artery followed by brisk pulsatile filling of the internal carotid, ophthalmic, and anterior cerebral arteries and the MCA. The initial arterial phase was followed by a parenchymal blush and subsequent venous phase. The entire sequence was completed in 12 seconds. Repeat DSA performed 30 minutes after injection of the clot embolus consistently showed nearly complete occlusion of the internal carotid artery at its junction with the circle of Willis (Fig. 1 upper right). Complete embolic occlusion resulted in a standing column of blood in the internal carotid artery with failure of angiographic visualization of its branches and lack of parenchymal blush. When DSA was repeated in the same animal 90 minutes after onset of treatment with intravenous TPA, return of dye flow was demonstrated (Fig. 1 lower left). During each DSA study, contrast enhancement of the MCA and parenchyma was measured and compared to the background noise within preselected ROI over the proximal MCA and the underlying parenchyma (Fig. 1 lower right). Contrast enhancement was quantitated by computer, based on the degree of x-ray attenuation that was proportional to the amount of Renografin passing through each ROI at each second during the study (Fig. 2). The data extrapolated in this fashion from the animal presented in Fig. 1 are plotted in Fig. 2 and show the iodine concentrations of the MCA ROI and parenchymal ROI in a temporal sequence (from left to right) for baseline, 30 minutes after embolus, and 90 minutes after initiation of TPA treatment. Similar curves were obtained in the other seven TPA-treated animals. The six control animals showed minimal change between the DSA studies performed after clot embolization and 90 minutes after onset of saline treatment.

The area under each iodine concentration curve was calculated as a measure of blood flow in the MCA ROI and tissue perfusion in the parenchymal ROI. Blood flows and tissue perfusion for each animal at 30 minutes after clot embolization and 90 minutes after initiation of treatment (120 minutes into the experiment) were then presented as percentage of change from baseline for each of the two treatment modalities (Fig. 3). The control group showed little change in MCA blood flow after saline treatment: no animals returned to baseline flow and the greatest improvement was 7.3% in one animal. The MCA values of the TPA-treated animals all returned to a minimum of 80% of baseline calculated flow, and one-half of the animals showed return of flow to greater than 100% of baseline (Fig. 3 left). The TPA-treated group had a mean calculated blood flow of 30.1% of baseline at 30 minutes after clot embolization and improved to a mean of 118% of baseline by 90 minutes after treatment. Comparison of

§ Videoplanometry unit manufactured by Carl Zeiss, Inc., Thornwood, New York.
TABLE 1

<table>
<thead>
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<th>Animal Group</th>
<th>Level of Consciousness</th>
<th>Response to Threat</th>
<th>Motor Function</th>
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<tr>
<td>control (6 rabbits)</td>
<td>Alert</td>
<td>Lethargic</td>
<td>Startle</td>
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<tr>
<td>TPA-treated (7 rabbits)</td>
<td>7</td>
<td>0</td>
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* TPA = tissue-type plasminogen activator.

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the mean calculated flows at 30 minutes in the control group (24.3%) and TPA-treated group (30.1%) showed no statistical difference. The statistical difference in the 90-minute mean calculated MCA flows for the control group (19.8%) and the TPA-treated animals (118%) was highly significant (p = 0.001).

Similar results were obtained with the calculated perfusion in the parenchymal ROI. The control group showed little change after saline treatment, with no animals returning to baseline flows. Parenchymal perfusion in all the TPA-treated animals returned to a minimum of 89% of baseline, and one-half of the animals showed return of perfusion to greater than 100% of baseline (Fig. 3 right). The TPA-treated group had a mean calculated perfusion of 33.4% of baseline at 30 minutes and improved to a mean of 104% of baseline after treatment. Comparison of the mean calculated perfusions at 30 minutes in the control group (29.3%) and the TPA-treated group (33.4%) showed no statistical difference. The statistical difference in the calculated parenchymal perfusion for the control group (19.1%) and the TPA-treated animals (104%) was highly significant (p = 0.001).

The neurological status was assessed by an observer 24 hours after clot injection. In the control group, five animals were lethargic and one was alert; the seven experimental animals were all alert. One-half of the control group did not startle in response to either a loud noise or a visual threat. Motor strength of the hind legs and ataxia were unchanged in all animals in both groups (Table 1). One animal in the TPA-treated group died overnight due to exsanguination from the femoral catheter.

Figure 4 shows representative premortem dye studies of midparietal slices of brain stained with Evans blue or neutral red dye in separate control animals. The Evans blue-stained slice shows blood-brain barrier breakdown and increased staining in the left parietal cortex. The left basal ganglia and cerebral cortex show decreased perfusion in the neutral red specimen. Both studies are consistent with angiographic evidence of internal carotid artery obstruction. Videoplanometric analysis was performed of the stained area of brain slices prepared with Evans blue dye or the absence of staining in slices prepared with neutral red dye. These areas were considered to show evidence of pathological change. The control group showed staining with Evans blue dye predominantly in the parietal and temporal regions. The TPA-treated group had significantly smaller areas of Evans blue staining (p = 0.05). The neutral red studies revealed decreased dye flow to areas of angiographic occlusion, specifically to the parietal and temporal lobes and the basal ganglia in the control group. All slices except the temporal tip showed significantly decreased staining (p = 0.05) in the control group as compared to the TPA-treated group (Table 2).

FIG. 3. Calculated blood flow versus time curves obtained from the middle cerebral artery (left) and parenchymal (right) regions of interest at the time of maximal occlusion (30 minutes) and after treatment with tissue-type plasminogen activator (TPA) (120 minutes). *Left: In the upper panel, saline-treated controls showed mean perfusion values 24.4% and 19.8% of baseline flow at 30 and 120 minutes, respectively. The TPA-treated rabbits (lower panel) were comparable at 30 minutes (30.1%) but showed nearly a fourfold increase of baseline flow to 118% at 120 minutes. Comparison of the control with the TPA-treated group was significant (p = 0.001). Right: In the upper panel, saline-treated control animals showed mean perfusion values of 29.3% and 19.1% of baseline at 30 and 120 minutes, respectively. The mean parenchymal perfusion in TPA-treated rabbits (lower panel) was 33.4% at 30 minutes and showed a threefold increase to 104% of baseline flow at 120 minutes. Comparison of the control with the TPA-treated group was significant (p = 0.001).*

Discussion

Two recent experimental DSA studies in dogs verified the validity of computer analysis to assess coronary artery flow and myocardial perfusion.12,17 We have applied this technique to the cerebral circulation and have documented three findings. First, blood flow through...
FIG. 4. Representative midparietal slices of brain stained with Evans blue dye (left) and neutral red dye (right) in separate control animals. The Evans blue-stained slice shows blood-brain barrier breakdown and increased staining in the left parietal cortex. The neutral red-stained specimen shows decreased perfusion and staining in the left basal ganglia and cortex. Both are consistent with angiographic evidence of internal carotid artery obstruction.

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<th>Table 2</th>
<th>Planometric results of staining in control and TPA-treated rabbits</th>
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<td>Slice Location</td>
<td>Slice Area (sq cm)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>posterior parietal</td>
<td>1.39 ± 0.32</td>
</tr>
<tr>
<td>midparietal</td>
<td>1.52 ± 0.25</td>
</tr>
<tr>
<td>temporal tip</td>
<td>1.42 ± 0.38</td>
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*Values are areas measured in sq cm; numbers in parentheses indicate percent of slice with abnormality as compared to the slice area. All values except the temporal tip in the neutral red-stained slices show statistical significance (p = 0.05, Student’s t-test). TPA = tissue-type plasminogen activator.

previously occluded vessels is improved significantly by TPA treatment (p = 0.001). Second, in this ischemic model the perfusion of brain parenchyma closely parallels the flow in the feeding blood vessel. Third, treatment with TPA, as compared to saline, resulted in significant improvement in parenchymal perfusion (p = −0.001) and in one-half of the cases after ischemic hyperperfusion. These findings establish the effectiveness of intravenous TPA therapy as treatment in acute embolic stroke due to clot embolization, and confirm the previous experimental results of Zivin, et al.,20 and Penar (unpublished data, 1986).

The neurological examination performed 24 hours after treatment revealed a decreased level of consciousness and responsiveness to threat in saline-treated animals. It is noteworthy that, despite evidence for diffuse neurological damage in saline-treated animals, no gross motor deficits were recorded; this may reflect on the limitation of our grading scale. There were statistically significant differences in Evans blue and neutral red staining in TPA-treated versus control animals (p = 0.05). Evans blue dye was used as a marker of blood-brain barrier damage, and the smaller area of staining in TPA-treated animals implied decreased breakdown as compared to the control group. Tissue perfusion is required for neutral red staining of brain, and TPA-treated animals demonstrated significantly smaller areas of lack of staining, indicating better perfusion in these animals 24 hours after treatment as compared to the control group. These findings are in agreement with the demonstrated improved flow on DSA studies in the TPA-treated animals. Furthermore, these results support the position that cerebral tissue may be more resistant to ischemia than has been historically recognized and that, for at least a limited period of time (up to several hours), the cerebral blood flow may drop below a level necessary for neuronal function but may still temporarily maintain neuronal viability. Thrombolytic intervention during this period of time may result in recovery or diminution of neurological deficit.

Since stroke is the third leading cause of morbidity in the United States and up to 60% of strokes are reportedly of embolic origin, potentially a large population of patients could benefit from reestablishment of blood flow to ischemic areas of the brain within a critical time period. Although most such emboli are not composed purely of blood clots, the intravascular clot propagation that develops subsequent to an embolic atheroma adds to the severity of the regional ischemia and the resultant tissue damage and neurological deficit. Thrombolytic intervention may therefore be of benefit in reducing the ischemic damage in such patients and...
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may possibly provide time for consideration of surgical
eMBOLecomy in selected cases. However, a number of
concerns must be evaluated prior to any human studies.
The risk of converting a bland infarct into a hemor-
rhagic one needs further investigation. A recent review
of clinical experience with intra-arterial thrombolytic
agents by Del Zoppo, et al., suggested an incidence of
postreperfusion hemorrhage of about 13%. Intravenous
administration of fibrin-specific short-acting thrombo-
lytic agents such as TPA may, however, reduce the
incidence of this complication. The specific drug regi-
men and the critical period of time for initiation of

Finally, studies are needed to establish the relation-
ship between cerebral reperfusion and the pattern of
neuronal recovery. In our laboratory we are presently
studying the cerebral high-energy phosphate metabo-
lism in response to reestablishment of cerebral perfu-
sion, and the time factors involved in recovery.

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ogen activator reduces neurological damage after cerebral

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