Tolerance of the Cerebral Venous System to Retrograde Perfusion Pressure in Focal Cerebral Ischemia in Rats

Takashi Ueda, MD, Y. Lucas Yamamoto, MD, PhD, Eiichi Takara, MD, and Mirko Diksic, PhD

Using quantitative double-tracer autoradiography, we examined the tolerance of the rat cerebral venous system in focal cerebral ischemia to retrograde perfusion pressure into the inferior cerebral vein. At perfusion pressures of <150 mm Hg, there was no significant change in local cerebral blood flow (LCBF) and blood–brain barrier (BBB) permeability. At pressures of >170 mm Hg, significant changes occurred in BBB permeability in the superficial cortical layers and there was a mild reduction of LCBF. In the group of rats subjected to 200 mm Hg perfusion pressure, the change in BBB permeability extended to the entire cortical zone and significant reduction of LCBF occurred. Our results indicate for the first time that during conditions of focal cerebral ischemia, the rat cerebral venous system can tolerate up to 150 mm Hg of retrograde perfusion pressure into the cerebral venous system without any change in BBB permeability or in LCBF. However, progressive change in BBB permeability and reduction in LCBF occur once the perfusion pressure exceeds 170 mm Hg. This finding may permit more efficient delivery of cytoprotective agents into ischemic tissue. (Stroke 1989; 20:378–385)

The clinical and laboratory observation that brain cells are more resistant to ischemia than previously assumed has stimulated considerable investigation into not only factors responsible for irreversible ischemic cell damage but also ways to improve cell function in the ischemic penumbra.1–11 Since the common pathophysiologic abnormality in acute cerebral ischemia is a significant reduction in the arterial blood supply to brain tissue, due to either atherosclerotic narrowing or sudden occlusion of a major supplying artery, it is often difficult to supply adequate amounts of promising cytoprotective agents systemically or arterially to the ischemic tissue. Fortunately, however, the cerebral venous system has rich microcollateral channels12–15 and is subject to minimum atherosclerotic changes.16,17 We have therefore explored the cerebral venous system as a new supply route to deliver blood and cytoprotective agents to ischemic brain tissue.

A sudden increase in arterial blood pressure can cause changes in the permeability of small cerebral vessels,18–21 including the venules.22–26 The tolerance of the cerebral venous system during conditions of focal cerebral ischemia to retrograde perfusion pressure into the cerebral vein remains unknown, however. We examined this tolerance by occluding the middle cerebral artery (MCA) of rats and using quantitative double-tracer autoradiography with [18F]fluoroantipyrine ([18F]FAP) to measure local cerebral blood flow (LCBF)27 and with [14C]a-aminoisobutyric acid ([14C]AIB)28,29 to measure blood–brain barrier (BBB) permeability.

Materials and Methods

We used 30 adult male Sprague-Dawley rats weighing 320–400 g. In 27 rats, we determined the blood-to-brain transfer constant (k) and LCBF. Cerebral ischemia was produced in 21 of these by occlusion of the left MCA,30 and 1 hour later transvenous perfusion of the brain (TVPOB) was started. The rats were divided into four experimental groups, depending on the perfusion pressure of TVPOB: six rats with 100 mm Hg, six with 150 mm Hg, three with 170 mm Hg, and six with 200 mm Hg. A sham-operated control group comprised

From the Cone Neurosurgical Research Laboratory and Neuroradiology Laboratory, Montreal Neurological Institute, McGill University, Montreal, Canada.

Supported by Medical Research Council of Canada Grant MT-3174 and the Killam Scholarship Fund of the Montreal Neurological Institute.

Address for reprints: Dr. Y.L. Yamamoto or Dr. M. Diksic, Montreal Neurological Institute, 3801 University Street, Room 636, Montreal, Quebec, Canada H3A 2B4.

Received April 26, 1988; accepted July 26, 1988.
six rats that underwent the same anesthesia, surgical procedures, and cannulation into the cerebral vein as the ischemic groups but did not undergo TVPOB. We measured changes in the cortical venous pressure before and after MCA occlusion in three rats that underwent only the anesthesia and cannulation into the cerebral vein.

The rats were fasted overnight, with water provided ad libitum, before the experiment. Under general anesthesia with 1.5–2% halothane, a tracheostomy was made and each rat was connected to a Harvard rodent respirator (Harvard Instruments, South Natick, Massachusetts) to maintain arterial blood gases within physiologic ranges as monitored by a blood gas analyzer (Model 1302, Instrumentation Laboratory Systems, Lexington, Massachusetts). Following catheterization of the femoral vessels with PE-50 tubing, a small cranietomy was made using a dental drill under a dissecting microscope. A 2×2-mm piece from the inferior and posterior part of the squamosal bone was removed just posterior to the postglenoid foramen. The inferior cerebral vein, anatomically comparable to Labbé’s vein in humans, collects venous blood from the centroparietotemporal regions. Using a fine catheter, we cannulated the inferior cerebral vein backwards to the ischemic area created by occlusion of the MCA. The midpoint of the vein was punctured by a 30-gauge needle and immediately cannulated backwards toward the sylvian area with the tapered tip of a PE-10 polyethylene catheter (i.d. 0.28 mm, o.d. 0.61 mm). After the catheter was inserted into the inferior cerebral vein, the puncture was covered with a small piece of oxidized cellulose and Gelfoam added to a drop of Krazy Glue (Chicago, Illinois) to prevent blood leakage. The PE-10 catheter was then connected to the conduit system, which consisted of three three-way stopcocks. To avoid blocking the catheter and conduit system, <0.1 ml heparinized saline was infused intermittently at <30 mm Hg perfusion pressure until the beginning of the autologous blood infusion. The left MCA was then occluded by a Zen clip (Netheler & Hinz GmbH, Hamburg, FRG). The surgical wounds were anesthetized locally with 2% xylocaine jelly and solution, and then the general anesthesia was switched to 50 mg/kg i.m. ketamine and 8 mg/kg i.m. xylazine every hour during the entire experiment to minimize hemodynamic and metabolic effects while maintaining adequate anesthesia. Finally, 0.5 mg/kg i.m. atropine was injected to prevent cholinergic reaction.

The systemic arterial blood pressure was monitored with a physiologic transducer (Transect, Bently-Transect Corp., Irvine, California). Hematocrit was determined intermittently in arterial blood samples using an Eppendorf Geratebau Model 5412 centrifuge (Netheler & Hinz GmbH, Hamburg, FRG). Body temperature was continuously monitored with a rectal temperature probe and held at 37±0.4°C by means of a heating lamp positioned over the rat. TVPOB was started 1 hour after the occlusion of the MCA and ended with decapitation 3 hours after the occlusion. Autologous arterial blood was infused continuously into the cerebral vein at perfusion pressures of 100, 150, 170, and 200 mm Hg; the respective autologous blood infusion rates were 0.17, 0.2, 0.25, and 0.28 ml/min. To replenish the blood in the conduit system, the heparinized arterial blood was withdrawn from the femoral artery 1 ml each time and at rates similar to the TVPOB infusion rate. The infusion pressure was obtained by compressing a polyvinyl chloride bottle filled with 0.9% saline using a mercurial sphygmomanometer (Tycos, Taylor Instrument Co., Asheville, North Carolina) that was connected at the distal end of the conduit system; infusion pressure was gradually increased in a stepwise fashion (20–30 mm Hg at each step, approximately 5 minutes between steps) from 0 to the desired pressure. During the infusion, the catheter and conduit system were always filled with autologous blood, which was replaced periodically according to the infusion schedule described above. The infusion pressure was constantly measured through the proximal three-way stopcock in the conduit system by the same transducer mentioned above. Pressure was maintained within 5 mm Hg using the high-pressure range of the blood pressure monitor (Sirecust 322, Siemens Energy & Automation, Inc., Cherry Hill, New Jersey) during TVPOB.

The quantitative double-tracer autoradiographic technique for the simultaneous measurement of LCBF and local BBB permeability used [18F]FAP and [14C]AIB. It has been described in detail,27 but briefly, the method is based on the difference in the physical half-lives of two tracers, fluorine-18 (T1/2 = 110 minutes, Emax = 240 keV) and carbon-14 (T1/2 = 5730 years, Emax = 45 keV).

An LCBF autoradiogram using [18F]FAP (the first exposure) was obtained by immediate 2-hour exposure of brain sections to Kodak SB-5 film (Rochester, New York). Fluorine-18 autoradiograms had <2% contamination from carbon-14.27 Three days later, when fluorine-18 had decayed completely, a BBB permeability autoradiogram for tissue distribution of [14C]AIB (the second exposure) was made by exposing the same brain sections to Kodak SB-5 film for 2–3 weeks.

We used the quantitative autoradiographic method developed by Blasberg et al.28,29 to study the cerebral microvascular permeability, that is, to measure BBB. Reliable k5 can be determined from data obtained in single-time experiments.29 Thirty to fifty microcuries of [14C]AIB (specific activity 55 mCi/mM, American Radiolabeled Chemicals Inc., St. Louis, Missouri) in 1 ml normal saline was injected intravenously with a constant infusion. Fifty-microliter arterial blood samples were drawn 0.25, 0.5, 1, 2, 3, 5, 7.5, 10, 15, 20, 25, and 30 minutes after the injection of [14C]AIB and centrifuged imme-
Immediately. Twenty microliters of plasma was then pipetted from each sample into counting vials. Rats were decapitated 30 minutes after the injection of [¹⁴C]AIB. The radioactivity of carbon-14 was measured 3 days (39 half-lives of fluorine-18) later using a liquid scintillation counter (1219 Rackbeta Liquid Scintillation Counter, Wallac Oy, Turku, Finland). The $k_j$ for each locus was calculated from the tissue carbon-14 concentration $[C(T)]$ at the end of the experiment and the arterial plasma carbon-14 concentration $[C_p]$-time integral as

$$C(T) = \int_0^T C_p \, dt$$

where $T$ is the duration of the experiment in minutes.

To measure LCBF, 29 minutes after the injection of [¹⁴C]AIB, 3–5 mCi of [¹⁸F]FAP (specific activity approximately 600 mCi/mM) prepared at the Medical Cyclotron Unit of the Montreal Neurological Institute was constantly infused intravenously for approximately 600 mCi/mM. Values of $\Delta^T$ in regions of interest were determined by Sako et al. The brain–blood partition coefficient of 0.89 for [¹⁸F]FAP determined by Sako et al. was used.

The optical density was measured six times with a photovolt densitometer (Sargent-Welch Densi
counter (Model 250, Baird-Atomic Inc., Cambridge, Massachusetts) with a multichannel analyz
ner (TN-7200, Tracor Northern, Inc., Middleton, Wisconsin). LCBF was calculated using the oper
equation described by Sakurada et al. The brain–blood partition coefficient of 0.89 for [¹⁸F]FAP

Results

As shown in Table 1, blood gases, blood pressure, and hematocrit remained within the normal
ranges in all rats throughout the study. There was no significant difference in these parameters between
the sham-operated and the TVPOB-treated groups.

After cannulation into the cerebral vein, the increase in BBB permeability was minimal and was
confined to the left rhinal fissure over the surgical
site; this was observed in all rats. In rats treated
with TVPOB at pressures of < 150 mm Hg, there
were no significant changes in $\Delta^T$, in the entire
ischemic cerebral hemisphere except over the sur-
gical site (Figure 1, A and B). TVPOB with 200 mm Hg perfusion pressure resulted in marked and widespread increases in $\Delta^T$ values in the entire cortical layers of the ipsilateral auditory cortex (Table 2), but the high values were
localized in and around the perfused site (Figure 1C). TVPOB with 200 mm Hg perfusion pressure
resulted in marked and widespread increases in $\Delta^T$ values in the entire cortical layers of the ipsilateral auditory, sensory motor, occipital, and auditory cortices (Table 2, Figure 1D).

LCBF was severely reduced in the left insular and perirhinal cortices over the surgical site in all rats. LCBF in the sensory motor and parietal cor-

\begin{table}
<table>
<thead>
<tr>
<th>Variables</th>
<th>Control, 6 mm Hg (n=6)</th>
<th>100 mm Hg (n=6)</th>
<th>150 mm Hg (n=6)</th>
<th>170 mm Hg (n=3)</th>
<th>200 mm Hg (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>116±9</td>
<td>114±5</td>
<td>111±10</td>
<td>112±9</td>
<td>115±25</td>
</tr>
<tr>
<td>PacO₂ (torr)</td>
<td>39.8±3.5</td>
<td>39.5±2.4</td>
<td>40.6±3.7</td>
<td>40.2±3.0</td>
<td>40.2±3.4</td>
</tr>
<tr>
<td>PaO₂ (torr)</td>
<td>115±10</td>
<td>118±11</td>
<td>110±9</td>
<td>108±10</td>
<td>109±9</td>
</tr>
<tr>
<td>pH</td>
<td>7.41±0.05</td>
<td>7.42±0.03</td>
<td>7.39±0.06</td>
<td>7.41±0.03</td>
<td>7.41±0.04</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>47±1</td>
<td>47±1</td>
<td>48±3</td>
<td>47±2</td>
<td>47±2</td>
</tr>
<tr>
<td>Values are mean±SD; TVPOB, transvenous perfusion of the brain; MABP, mean arterial blood pressure. No significant change in any variable occurred during the experiment.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 1. Autoradiographic images of [14C]-a-aminoisobutyric acid from coronal section of thalamus/parietal cortex region. Small increases of transfer constant (Ki) appear only in subpial portion of left rhinal fissure at operative site in rats receiving transvenous perfusion of brain at 100 mm Hg (A) and 150 mm Hg (B) perfusion pressure. However, there is a significant increase of Ki in the superficial layers of left auditory cortex in rat treated at 170 mm Hg (C) and widespread, marked increase of Ki in the entire cortical layers of left auditoparietal cortices in rat treated at 200 mm Hg perfusion pressure (D).

texes was elevated above control levels, but there was no significant difference between the control group and the groups receiving TVPOB at perfusion pressures of 100 and 150 mm Hg (Figure 2, Table 3). In the 170 mm Hg group there were, however, significant reductions of LCBF in the auditory cortex (36% reduction, p<0.05). In the 200 mm Hg group there was a marked increase of Ki in the left parietal cortex and LCBF in the entire cortical layers of left auditory cortex (p<0.01). The Ki values and LCBF in that area were not significantly different between the control group (k, 1.4±0.2×10⁻³ ml/g/min, LCBF 25±6 ml/100 g/min) and the groups treated with TVPOB at pressures of 100 mm Hg (k, 1.5±0.3×10⁻³ ml/g/min, LCBF 29±7 ml/100 g/min) and 150 mm Hg (k, 1.4±0.5×10⁻³ ml/g/min, LCBF 28±12 ml/100 g/min). However, when the pressures of TVPOB were increased to 170 mm Hg, k, in the left auditory cortex was elevated to 3.3 times (4.6±1.6×10⁻³ ml/g/min, p<0.01) that of the control group. In contrast, LCBF in the same area was reduced, significantly, to 16±7 ml/100 g/min (36%, p<0.05). In the group receiving TVPOB at a pressure of 200 mm Hg, k, and LCBF in most cortical areas of the left cerebral hemisphere were markedly changed; k, was four times (5.6±2.7×10⁻³ ml/g/min) that of the control group (p<0.01) and LCBF was 48% less than that of the control group (13±6 ml/100 g/min, p<0.01). There was no significant change of LCBF in the ipsilateral subcortical areas or the contralateral hemisphere in the TVPOB-treated groups compared with the control group.

In three rats, the cortical venous pressure was 12.5±3.4 mm Hg after cannulation and before MCA occlusion. After MCA occlusion, the pressure was rapidly decreased: 5.8±2.3 mm Hg at 1 minute, 4.8±1.0 mm Hg at 5 minutes, and 3.3±0.3 mm Hg at 10 minutes. It settled at 3.7±1.2 mm Hg at 20 minutes and remained there for 3 hours. Therefore, there was a significant reduction (72%) of venous pressure after the MCA occlusion.

Discussion

A sudden increase in arterial blood pressure can cause permeability changes in the cerebral small vessels,18-21 including the venules.22-26 Unfortunately, there is little data available on the physiologic tolerance of the cerebral venous system.35,36 To our knowledge, few experimental studies have been done on transvenous retrograde perfusion of the brain.36 In particular, there was no study reported on the maximum tolerance to retrograde perfusion pressure
Table 2. Effect of TVPOB on Transfer Constant Under Left Middle Cerebral Artery Occlusion in Ischemic Hemisphere of Rats

<table>
<thead>
<tr>
<th>Structures</th>
<th>Control, 0 mm Hg (n=6)</th>
<th>TVPOB-treated groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mm Hg (n=6)</td>
<td>150 mm Hg (n=5)</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>1.2±0.2</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Sensory motor cortex</td>
<td>1.3±0.1</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>1.2±0.3</td>
<td>1.4±0.1</td>
</tr>
<tr>
<td>Auditory cortex</td>
<td>1.4±0.2</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>1.1±0.2</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.8±0.3</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.0±0.3</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>0.8±0.3</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Medial</td>
<td>0.9±0.4</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>0.8±0.4</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>0.8±0.3</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Medial</td>
<td>0.9±0.4</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>6.3±4.8</td>
<td>5.6±2.5</td>
</tr>
<tr>
<td>Dentate</td>
<td>0.8±0.4</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Pineal</td>
<td>31.8±6.1</td>
<td>28.2±2.3</td>
</tr>
</tbody>
</table>

Values are mean±SD×10⁻³ ml/g/min. TVPOB, transvenous perfusion of the brain.
*tp<0.05, 0.01, respectively, different from control by two-tailed unpaired t test.

Figure 2. Autoradiographic images of [¹⁸F]fluorooxypyrine from coronal section of thalamus/parietal cortex region showing local reduction of cerebral blood flow (LCBF) in left insular and perirhinal cortices at operative site in all rats. There is no significant difference of LCBF between control rats and those treated with transvenous perfusion of brain at 100 mm Hg (A) and 150 mm Hg (B) perfusion pressure. However, there is a moderate reduction (38%) of LCBF in left auditory cortex at 170 mm Hg (C) and severe reduction (50%) of LCBF in left auditoparietal cortices at 200 mm Hg (D) compared with controls.
of the cerebral vein. Therefore, we attempted to establish in rats the optimal and maximum tolerance of retrograde perfusion pressure for TVPOB with quantitative double-tracer autoradiography, in which LCBF was measured with \[^{[18F]}\text{FAP}\] and BBB permeability with \[^{[14C]}\text{AIB}\]. This permitted evaluation of a correlation between LCBF and BBB permeability changes in the same tissue section, thus providing reliable information enabling us to define an optimal perfusion pressure for TVPOB.

Our results showed that in rats with TVPOB at perfusion pressures of <150 mm Hg there was no change in BBB permeability. Our previous study in dogs\(^{37}\) indicated that simultaneous occlusion of several cortical veins induced perivenous leakage of fluorescein dye and a reduction of LCBF because of increased venous pressure and a reduction in the number of collateral venous pathways but that occlusion of one large draining vein alone did not cause a change in BBB permeability or any reduction of LCBF due to the rich venous collateral channels in the cerebrum.\(^{15,38}\)

Ablation elevation of the systemic arterial blood pressure induced by intravenous injection of metaraminol bitartrate in cats resulted in extravasation of Evans blue from the small cerebral vessels with increased cerebral venous pressure.\(^{18}\) However, stepwise elevation did not change BBB permeability in the small cerebral vessels in cats.\(^{19,20}\) The percent and rate of the increase in pressure are therefore more important than the absolute pressure. Denny-Brown et al\(^{36}\) reported that a sudden retrograde injection of saline into a cortical vein in monkeys under normal conditions resulted in the abrupt appearance of complete ischemia in the cortical area. No actual pressure measurements were recorded during perfusion of the vein, but it was estimated that a pressure of >50 mm Hg was necessary.\(^{36}\) Recently, we investigated the physiologic integrity of the epicerebral venous system by means of retrograde cerebral fluorescein venography in dogs. Fluorescein dye leaked heavily from the epicerebral veins following an abrupt infusion at pressures estimated to be >160 mm Hg. Leakage was not observed, however, following a stepwise increase of perfusion pressure below 80 mm Hg.
during retrograde infusion. These results suggest that the cerebral vessels are more tolerant of a stepwise increase of intraluminal pressure, so we increased pressure in a stepwise fashion for this study.

There have been numerous investigations of alterations in the cerebral circulation following occlusion of the MCA, but few have focused on changes in the cerebral venous system. In rats, we have observed that cortical venous pressure declined significantly from 12.5 to 3.7 mm Hg following MCA occlusion. Symon also measured the cortical arterial and venous pressures directly before and after MCA occlusion in baboons. He reported that the mean MCA pressure before the occlusion was 94.3 mm Hg and the mean venous pressure of the branch of the middle cerebral vein was 14.4 mm Hg. Occlusion of the MCA caused a fall in mean pial arterial pressure (20.6 mm Hg) and mean venous pressure (9.4 mm Hg). The significant reduction of the microcirculatory resistance following occlusion of the MCA may explain why the cerebral venous system can tolerate up to 150 mm Hg retrograde perfusion pressure after MCA occlusion.

In rats with occlusion of the MCA treated by TVPOB at 170 mm Hg perfusion pressure, BBB permeability increased in the ipsilateral auditory cortex; however, the superficial layers within 1 mm of the cerebral surface. TVPOB at 200 mm Hg perfusion pressure resulted in marked and widespread increases in \( k_i \) in the ipsilateral cerebral hemisphere over the entire cortical zone extending into the white matter. The breakthrough point of BBB permeability for retrograde perfusion into the cerebral vein may lie between pressures of 150 and 170 mm Hg in rats with focal ischemia induced by occlusion of the MCA. Duvernoy described "superficial vascular pathways" and "deep vascular pathways" in the human brain. The vascular supply of the hemispheric cortex was reported to be similarly organized in rats and humans. Our results with TVPOB at 170 mm Hg pressure indicate that the small vessels in the superficial vascular pathways are more vulnerable to retrograde perfusion pressure than the deeply penetrating large vessels.

Our results indicate for the first time that the cerebral venous system in rats can tolerate up to 150 mm Hg retrograde perfusion pressure into the cerebral venous system without any change in BBB permeability or LCBF. However, once the pressure exceeds 170 mm Hg, BBB permeability is altered and LCBF declines. Our new TVPOB method thus makes it possible to deliver cytoprotective agents into ischemic tissue more selectively and efficiently.

Acknowledgments

The authors would like to thank the members of the Medical Cyclotron Unit for the preparation of [\(^{18}\)F]FAP, Mrs. Janet Arts for technical assistance, and Miss F. Lumia for excellent typing.

References

12. Rowbotham GF, Little C: Circulations of the cerebral hemispheres. *Br J Surg* 1965;52:8–21


32. Shiue CY, Wolf AP: Synthesis of 4-fluoro-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one ($4$-fluoroantipyrine) and $^{3}$F-labeled analog by direct fluorination of antipyrine to molecular fluorine. *J Label Compds Radiopharm* 1981;18:1099–1106


**KEY WORDS** • autoradiography • blood-brain barrier • cerebral blood flow • rats
Tolerance of the cerebral venous system to retrograde perfusion pressure in focal cerebral ischemia in rats.
T Ueda, Y L Yamamoto, E Takara and M Diksic

Stroke. 1989;20:378-385
doi: 10.1161/01.STR.20.3.378

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/3/378

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/