Hyperglycemia Enlarges Infarct Size in Cerebrovascular Occlusion in Cats

Gabrielle de Courten-Myers, MD, Ronald E. Myers, MD, PhD, and Lydia Schoolfield, BS

We investigated the influence of serum glucose concentration on infarct size following middle cerebral artery occlusion in cats. These animals were deprived of food for 48 hours and infused with 1) saline for 1 hour before and 8 hours after occlusion (n = 8), 2) 10% glucose solution for 1 hour before and 6 hours after occlusion and saline for 2 additional hours (n = 8), or 3) 10% glucose for 1 hour before and saline for 8 hours after occlusion (n = 5). Nineteen cats killed after 2 weeks' survival were subjected to morphometric infarct size determinations. Eight normoglycemic and 11 hyperglycemic cats exhibited infarcts affecting 10.2 ± 3.4% and 29.5 ± 6.5% (mean ± SEM) of their middle cerebral artery territories, respectively (p < 0.02). Cats of the two hyperglycemic groups showed similarly sized infarcts. However, two of eight (25%) of cats with preocclusion and postocclusion hyperglycemia died 8 and 24 hours after occlusion with infarction of the entire middle cerebral artery territory, marked hemispherical edema, and brainstem compression. Our results demonstrate that serum glucose concentration at the time of large cerebral vessel occlusion influences stroke outcome. (Stroke 1988;19:623–630)

Serum glucose concentration has only recently been proposed as a factor that may affect stroke outcome. Such an influence may be suspected because experimental studies have demonstrated that elevated serum glucose concentrations strikingly reduce brain tolerance to circulatory arrest and other forms of systemic hypoxia-ischemia. In the anoxic brain, hyperglycemia exerts its detrimental effect by increasing the amount of substrate for glycolysis and thus accentuating brain tissue lactic acidosis. Brain tissue acidosis closely correlates with development of edema that develops in 6–48 hours, whereas focal ischemia may lead to brain edema progressing over several days.

Our study was designed to shed more light on this issue by investigating the role played by different serum glucose concentrations in influencing the size of infarcts produced by occlusion of the middle cerebral artery (MCA) in cats.

Materials and Methods

Thirty-three healthy, adult mongrel cats weighing 2.5–4.6 kg were used. The right MCA was permanently occluded using miniature Yasargil aneurysm clips. A transorbital approach served as the route for MCA exposure and occlusion under visual control through a surgical microscope.

Food deprivation. All cats were deprived of food for 48 hours before surgery to reduce liver glycogen stores to ensure greater stability of serum glucose concentrations during and after MCA occlusion. Such serum glucose concentration stability is particularly important in our study since it specifically investigates this variable's influence and since cats, more than other species, develop major hyperglycemia in reaction to stress.

Anesthesia. Pentobarbital, 35 mg/kg i.v., served as the anesthetic. This initial dose was supplemented by four 5-mg/kg doses administered twice before and 3 and 6 hours after MCA occlusion. The right femoral artery and vein were catheterized with heparinized PE-90 polyethylene catheters, the tips of which were advanced to lie in the thoracic aorta and inferior vena cava. The pulsatile and mean arterial (MABP) blood pressures and heart rate were continuously recorded on an eight-channel Gould polygraph (Cleveland, Ohio). Core body temperature was maintained at 38.5 ± 0.5°C. Penicillin/streptomycin, 100,000 units i.m., was given daily for 5 days starting the day of surgery.
Table 1. Physiological Parameters Monitored in Cats With Middle Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Class</th>
<th>Sample time (hr)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (kPa)</td>
<td>H</td>
<td>15.6±2.2</td>
<td>15.7±2.1</td>
<td>16.0±1.8</td>
<td>15.6±1.9</td>
<td>15.7±2.1</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15.4±1.9</td>
<td>16.0±2.4</td>
<td>15.8±2.5</td>
<td>16.4±1.9</td>
<td>16.9±3.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>H</td>
<td>195±42</td>
<td>205±38</td>
<td>208±36</td>
<td>217±36</td>
<td>213±39</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>176±32</td>
<td>191±21</td>
<td>218±68</td>
<td>206±86</td>
<td>208±86</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>H</td>
<td>37.8±0.6</td>
<td>38.2±0.5</td>
<td>38.3±0.4</td>
<td>38.5±0.6</td>
<td>38.7±0.7</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>38.4±0.8</td>
<td>38.4±0.3</td>
<td>38.4±0.6</td>
<td>38.5±0.6</td>
<td>38.9±0.5</td>
</tr>
<tr>
<td>pH</td>
<td>H</td>
<td>7.333±0.089</td>
<td>7.297±0.085</td>
<td>7.335±0.082</td>
<td>7.353±0.105</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>7.368±0.077</td>
<td>7.332±0.087</td>
<td>7.355±0.095</td>
<td>7.411±0.041</td>
<td></td>
</tr>
<tr>
<td>Pao₂ (kPa)</td>
<td>H</td>
<td>13.0±0.9</td>
<td>13.2±1.1</td>
<td>13.7±1.0</td>
<td>13.5±1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>12.7±0.7</td>
<td>13.1±1.2</td>
<td>13.5±1.6</td>
<td>13.1±1.0</td>
<td></td>
</tr>
<tr>
<td>Paco₂ (kPa)</td>
<td>H</td>
<td>5.0±0.7</td>
<td>4.8±0.9</td>
<td>4.5±0.8</td>
<td>4.4±1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>5.0±1.3</td>
<td>5.3±1.0</td>
<td>4.9±1.1</td>
<td>4.5±1.2</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>H</td>
<td>0.36±0.07</td>
<td>0.37±0.07</td>
<td>0.39±0.04</td>
<td>0.40±0.05</td>
<td>0.41±0.08</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>0.36±0.08</td>
<td>0.35±0.06</td>
<td>0.36±0.05</td>
<td>0.38±0.03</td>
<td>0.39±0.05</td>
</tr>
<tr>
<td>Serum lactate (mM/l)</td>
<td>H</td>
<td>0.8±0.8</td>
<td>0.9±0.8</td>
<td>1.0±1.0</td>
<td>0.8±1.0</td>
<td>0.8±1.0</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>1.6±0.6</td>
<td>1.3±0.5</td>
<td>1.4±0.6</td>
<td>1.3±0.6</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>Serum pentobarbital (µg/ml)</td>
<td>H</td>
<td>27.5±2.1</td>
<td>27.3±1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>29.8±1.7</td>
<td>27.3±2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. H, hyperglycemia, glucose infused (n = 13); N, normoglycemia, saline infused (n = 8); kPa, mm Hg × 0.1333.

Intravenous infusions. Intravenous infusions served to hydrate the cats and to achieve the classes of glycemia sought. Equal volumes (10 ml/kg/hr for 1 hour before and 5 ml/kg/hr for 8 hours after MCA occlusion) of physiological saline or 10% glucose solution were administered intravenously using an infusion pump. Under this regimen a 3-kg cat received 150 ml fluid over 9 hours. Normoglycemic cats received normotonic saline only (saline group, n = 13), while in hyperglycemic cats 10% glucose in water was substituted for 1 hour before and 6 hours after MCA occlusion (1-hour glucose group, n = 12) or for 1 hour before occlusion (1-hour glucose group, n = 8).

Transorbital middle cerebral artery occlusion. The procedures for MCA occlusion followed those described by O’Brien and Waltz26 and modified by Kamiyio and Garcia.27 The right periorbital region was approached by retracting the soft tissues posterior to the conjunctival cul-de-sac. After the vitreous and lens were aspirated, the optic foramen was exposed and collapsed by incising its superior surface. A 5 × 7 mm bone opening in the orbital roof dorsirolaterally to the optic foramen was fashioned using a dental burr. The dura was incised, and a miniature Yasargil aneurysm clip was positioned around the MCA after its isolation. Repair of the skin incisions was completed by sutures. The blood volume lost was estimated and replaced by citrated donor blood. The blood lost by sampling for biochemical analysis also was replaced by transfusions after each 1.3-ml sample. Ninety-five percent of cats are of the same blood type, rendering transfusions almost completely free of complications.28

Postocclusion monitoring. The infusion of fluids and the monitoring of physiologic parameters continued for 8 hours after MCA occlusion according to the schedule depicted in Table 1. Cerebrospinal fluid (CSF) was sampled from the cisterna magna using a 20-gauge spinal tap needle 0, 3, and 6 hours after occlusion. Serum and CSF samples were frozen at −70°C for later biochemical analysis. After the catheters were removed (8 hours after occlusion) the cats were placed in a temperature-controlled intensive care unit and frequently observed over the following 48 hours. To minimize serum glucose concentration fluctuations the cats were provided only water per os during the first postoperative day, milk on Day 2, and canned cat food from Day 3 on. Hand-feeding was provided if necessary. Fluid and food intakes were recorded, and the cats’ neurologic status were evaluated daily for 14 days.

Blood and cerebrospinal fluid samples. Arterial blood samples were analyzed on-line for pH, Pao₂, Paco₂, (adjusted for barometric pressure, body temperature, and hemoglobin content) using a Corning blood gas and pH analyzer (Corning, New York). Hematocrit was determined in duplicate at each sample time. Serum and CSF lactate concentrations were measured spectrofluorometrically in a reaction mixture containing 200 mM hydrazine, pH 9.7, 1.0 mM EDTA, and 0.2 mM NAD. The reaction was initiated by adding 7.8 units lactate dehydrogenase, and NADH fluorescence was read after 30 minutes.29 Serum pentobarbital concentration at MCA occlusion and 4 hours later were assayed using gas chromatography.30 The serum sample plus an internal standard (secobarbital) were extracted.
into toluene. The acidified extract was injected into the gas chromatograph, methylated, and separated on a Silar-10C column. Standard curves were used to determine pentobarbital concentrations. Serum and CSF glucose concentrations were analyzed using an automated Beckman glucose analyzer (Fullerton, California) based on a glucose oxidase enzymatic method.

**Brain perfusion-fixation.** The cats again were anesthetized with 40 mg/kg pentobarbital after 2 weeks’ survival. Their brains were fixed by intra vitam, in situ perfusion at 150 cm H₂O pressure with 10% buffered formalin. The brains were removed and postfixed for 2 weeks in the same fixative.

**Brain examination.** Gross, microscopic, and morphometric evaluations of the brain were carried out with the examiners blinded as to the cat’s experimental status. Aneurysm clip placement was verified and its major branch distribution and to provide information as to the completeness of vessel occlusion and the presence of anastomotic channels bypassing the occlusion site. The brain surface was examined and palpated for areas of softening. Zones of tissue injury were photographed and their extents were recorded. Hemispheric edema was evaluated based on the presence and extent of herniation of the posterior cingulate cortex (the structure at risk in this species) and the cerebellar vermis, the associated deformation of the upper midbrain, midline shift, and the reduction in size of the ventricles and subarachnoid space around the cerebral gyri. The brain was sliced into six standard coronal sections using fixed external landmarks. Grossly apparent lesions in each slice were described and photographed. The six standard coronal brain slices were embedded in paraffin, and whole-mount histologic sections were cut and stained with hematoxylin and eosin.

**Morphometric infarct size assessment.** A computer-assisted image analysis system (Bioquant) served to assess infarct volumes. The outlines of the infarct and of the intact parenchyma (excluding the ventricles) were traced separately with a light pen directly on the six standard histologic sections. Areas of both were derived by computer integration. Mean values from a minimum of three measurements were calculated. Infarct volume (proportional to measured areas from representative serial sections taken throughout the brain) was calculated as percent hemispheric volume (sum of intact and infarcted parenchyma) and converted to percent MCA territory by multiplying by 2. The factor of 2 is based on the volume of the MCA territory compared with that of the entire hemisphere based on quantitative of India ink injections of this vessel combined with analogous morphometric measurements. These measurements slightly underestimate tissue loss since they fail to take tissue collapse into account. Two cats that died of hemispheral edema 8 and 24 hours after occlusion were excluded from quantitative infarct size assessments since, regarding age, clarity of demarcation from normal tissue, and extent of edema, their infarcts did not compare with lesions in the brains of 2-week survivors.

**Experimental and control groups.** Sham-operated cats developed no gross and <1% of MCA territory microscopic brain lesions as determined by preliminary studies. Cats were randomly assigned to experimental groups following the recommendation of Hossman.31 Further, group assignment remained unknown to the surgeon throughout the operative procedures.

**Exclusion criteria.** All cats with values for any cardiovascular or blood compositional parameter outside of mean ± 2 SD were excluded from the study. Parameters that provided the basis for exclusion included serum pentobarbital levels, MABP, blood gases, body temperature, surgical blood loss (> 10 ml), or improper MCA clip placement. Decisions regarding exclusion were made without knowledge of the cat’s assignment to experimental group or pathologic outcome.

**Statistical analyses.** All data regarding parameters measured were checked for discrepant values and nonnormal distributions. Transformations were made where necessary. Infarct size and parameters monitored according to sample time were averaged for the two glycemia classes, and SD and SEM were calculated. Serum and CSF sample pairs were fitted for linear regression lines. One-way analysis of variance was used to assess differences between the two glycemia classes. When significant differences were found, a multiple range test was performed with Kramer’s modification for unequal group sizes.

**Results**

Twenty-one cats, 13 hyperglycemic and eight normoglycemic, met criteria for inclusion in the study; 12
Infusion of 10% glucose solution elevated serum glucose concentrations significantly above those of the saline-infused cats, as Figure 1 demonstrates. At occlusion, the three treatment groups exhibited the following mean ± SD serum glucose concentrations: 18.4 ± 6.4 mM in the eight 1 + 6-hour glucose cats, 22.1 ± 6.3 mM in the five 1-hour glucose cats, and 6.5 ± 2.3 mM in the eight saline cats. Simultaneous CSF and blood samples were drawn 0, 3, and 6 hours after MCA occlusion. The CSF glucose concentrations paralleled those of serum, with mean values of 8-10 mM (144-180 mg/dl) during the infusion of 10% glucose solution and of 4-5 mM (72-90 mg/dl) during the infusion of saline. Thus, 30 serum and CSF sample pairs from 12 cats showed a significant linear correlation (r = 0.75, p<0.01) when analyzed for glucose concentrations.

The nine parameters monitored for 1 hour before and 8 hours after MCA occlusion, each of which might affect infarct size, showed the mean ± SD values described in Table 1. The two glycemia classes showed no significant differences regarding these variables at any time. They also failed to exhibit consistent changes in their CSF lactate concentrations sampled over 6 hours following occlusion (mean ± SD in mM at 0, 3, and 6 hours after occlusion: hyperglycemic class (n = 5), 0.9 ± 0.4, 1.0 ± 0.2, and 1.2 ± 0.1; normoglycemic class (n = 3), 1.3 ± 0.2, 1.3 ± 0.4, and 1.3 ± 0.2).

All eight saline cats and all five 1-hour glucose cats survived and were killed after 2 weeks' survival. However, two of eight 1 + 6-hour glucose cats died of respiratory arrest, 8 and 24 hours after clip application. Both showed maximal infarcts of the right MCA territory associated with marked hemispheral edema, herniation of the posterior cingulate cortex past the tentorial edge, and herniation of the vermis.

The brains of the 19 cats killed after 2 weeks' survival showed well-demarcated areas of focal necrosis affecting the right hemispheres, with the remaining brain areas appearing normal both grossly and microscopically (Figure 2). In contrast, the brains of the two cats that died within 24 hours with a marked right hemisphere edema showed extensive zones of tissue softening grossly and of acute, ischemic neuronal necrosis and tissue edema microscopically, all restricted to but affecting practically the entire right MCA territory.

The 11 hyperglycemic cats (five 1-hour and six surviving 1 + 6-hour glucose) killed after 2 weeks' survival showed mean ± SEM infarct sizes (expressed as % MCA territory) of 29.5 ± 6.5% compared with the normoglycemic cats' infarct sizes of 10.2 ± 3.4%. Figure 3 illustrates this threefold difference in infarct size between the normoglycemic and hyperglycemic classes (p<0.02).

Continuing glucose infusion for 6 hours after MCA occlusion had little effect on infarct size, provided the cats survived. The brains of the six surviving 1 + 6-hour glucose cats showed a mean ± SEM infarct size of 30.5 ± 10.8%, whereas those of the five 1-hour glucose cats showed a value of 28.4 ± 7.6%. However, only cats hyperglycemic for the longer time died of hemispheric edema (two of eight). The existence of a clinically relevant, altered outcome (25% vs. 0% deaths) of the two glucose groups suggests that the prolonged hyperglycemic state may affect outcome, although the numbers are too small to reach significance.

Figure 4 depicts the infarct size distributions in the normoglycemic and hyperglycemic classes. Normoglycemic cats exhibited small and intermediate-sized infarcts. Contrasting with this, hyperglycemic cats showed infarcts that covered the entire spectrum from small infarcts to death from hemispheric edema accompanied by infarcts that affected the entire MCA territory. Hyperglycemic cats showed a nearly even distribution among all infarct sizes.

Postmortem India ink injection into the right internal carotid artery with the MCA clip in place demonstrated
that one third of the cats had clearly defined proximal collateral blood vessels that linked the right anterior cerebral artery with the MCA distal to the occlusion. This constellation was associated with small or medium-sized infarcts in all three treatment groups.

The topographic distribution of the infarcts produced by MCA occlusion was analyzed quantitatively in the surviving normoglycemic and hyperglycemic cats. This analysis demonstrated two correlations:

1) The frequency with which the cerebral cortex (CC), the white matter (WM), and the central gray nuclei (CG) in the center of the MCA supply territory were injured in the two classes are closely similar and of high order (hyperglycemia/normoglycemia: CC = 0.91/0.88, WM = 1.00/1.00, CG = 0.88/0.82). In the periphery of the MCA supply territory, however, the hyperglycemic cats showed higher incidences of CC and WM infarcts, while both classes had little damage to CG (hyperglycemia/normoglycemia: CC = 0.64/0.25, WM = 0.46/0.13, CG = 0.09/0.00).

2) The hyperglycemic and normoglycemic classes showed differences in average extents of infarcts in each of the six coronal brain sections. In the center of the MCA territory the infarct size difference was smaller (2:1) than in the periphery (5:1) (hyperglycemia/normoglycemia: center = 23%/10%, periphery = 10%/2% infarction).

Discussion

Our results demonstrate that elevated serum glucose concentration increases the extent of tissue damage from MCA occlusion as had earlier been shown in global anoxia-hypoxia-ischemia. Indeed, hyperglycemic cats developed infarcts that were three times larger than those of normoglycemic cats. Additionally, 25% of cats hyperglycemic for 1 hour before and 6 hours after MCA occlusion died of massive hemispheric edema and brainstem compression, an outcome no normoglycemic or transiently hyperglycemic cat showed. Our findings concur with those of several clinical studies investigating the effects of glycemia on stroke evolution, which have suggested that elevated glucose concentrations aggravate outcome.

Infarct size from occlusion of major cerebral blood vessels is multifactorially determined, with a number of factors acting in combination. Parameters shown to affect this outcome include blood pressure and blood volume, hematocrit as it affects blood viscosity, blood gases, particularly Paco₂, and level of anesthesia. Thus, we paid detailed attention to these and other variables such as animal health status and body temperature, and verified the completeness and location of occlusion to isolate the role of level of serum glucose concentration on outcome from focal ischemia.
A detrimental effect of elevated glucose concentrations on infarct size also seen in the study by Brint et al. is not observed universally. Ginsberg et al. reported smaller photochemically induced infarcts in hyperglycemic than in normoglycemic rats. They proposed that the end-arteriolar location of the thrombotic occlusion causing a steep transition between near-zero to normal blood flow may be the basis for the positive rather than negative effect of hyperglycemia. Nedergaard and Diemer similarly saw no difference between normoglycemic and hyperglycemic MCA occlusion in rats, whereas hypoglycemia reduced but chronic diabetes increased infarct size. On the other hand, Nedergaard described larger infarcts and increased blood–brain barrier damage after 10 and 15 minutes of temporary MCA occlusion in hyperglycemic than in normoglycemic rats. This brief occlusion leading to infarction in rats may indicate an important species difference from larger mammalian species. In contrast to that rodent model, major cerebrovascular occlusion can remain reversible in humans, cats, and monkeys for several hours. A major difference between rat versus cat or monkey MCA occlusion models may be the size of functionally impaired penumbral regions, which is very small in rats.

The lack of changes in cisterna magna CSF lactate concentrations 3 and 6 hours after MCA occlusion fails to reflect the locally marked tissue lactic acidosis developing in the ischemic territory in many animals investigated for topographic brain biochemical alterations after 4 hours of MCA occlusion (K.R. Wagner, R.E. Myers, M. Kleinholz, G.M. de Courten-Myers, unpublished data). The temporal changes in cisterna magna CSF lactate concentrations following experimental systemic hypoxic hypotension in cats also suggest that a correlation of CSF lactate concentration and resulting infarct size following cerebrovascular occlusion would not be likely even though that study showed a significant rise in CSF lactate in cats with but not in cats without brain injury. The reason is that increases in lactate concentrations are very short-lived and significant only during the initial 30 minutes after resuscitation, with subsequent normalization of CSF lactate values irrespective of development and extent of brain tissue damage. Thus, focal brain tissue lactic acidosis is unlikely to be detectable from distant CSF sample sites.

Barbiturates may affect infarct size whether administered before or after cerebrovascular occlusion. The barbiturates' protective effects are again evident when the infarct sizes of awake cats exposed to MCA occlusion are compared with those of our study (mean ± SD, % MCA territory 83.8 ± 44% awake; 29.5 ± 21.7% hyperglycemic anesthetized; 10.2 ± 9.7% normoglycemic anesthetized).

Hossmann and Schuier estimated that MCA occlusion in anesthetized cats leads to ischemic areas that average 34% of the hemispheric volume. Taking this into account, we suggest that only one seventh of the initially ischemic area ends up infarcted in normoglycemic cats and one half of that area in hyperglycemic cats. Thus, a considerable amount of brain initially experiencing ischemia may escape injury, with metabolic factors acting as modulators. Hence, cerebral ischemia, though a sine qua non for injury, may not account fully for pathologic outcome. A similar conclusion emerges in considering the marked differences in infarct size according to presence or absence of anesthesia in similar models of focal ischemia (see above). Similarly, Marcoux et al. found a poor correlation between regional cerebral blood flow in the range 5–15 ml/100 g/min and subsequent pathologic outcome, which included both injured and intact sites. Only blood flow reductions to <5 ml/100 g/min strongly correlated with infarction.

The mechanisms by which hyperglycemia enlarges the tissue zone undergoing infarction from focal ischemia have yet to be defined. A more marked focal tissue acidosis as a consequence of elevated brain tissue glucose concentrations in areas of critical focal ischemia may accentuate focal tissue edema and its spread to surrounding tissue areas. This possibility seems
plausible since tissue injury has been shown to correlate with suprathreshold tissue acidosis in global anoxia-ischemia. More marked focal edema, in turn, may initiate a vicious circle of progressive expansion of zones of severe ischemia by transforming areas with initially only functional impairments (penumbra) to regions of definitive infarction.

References
45. Nedergaard M: Transient focal ischemia in hyperglycemic rats is associated with increased cerebral infarction. Brain Res 1987;408:79–85

KEY WORDS: hyperglycemia • cerebrovascular disorders • cats
Hyperglycemia enlarges infarct size in cerebrovascular occlusion in cats.
G de Courten-Myers, R E Myers and L Schoolfield

Stroke. 1988;19:623-630
doi: 10.1161/01.STR.19.5.623

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/19/5/623