Experimental studies have shown that acute moderate hyperglycemia existing before global brain ischemia worsens neurological damage. A proposed mechanism for hyperglycemia-enhanced ischemic brain damage is that, in the presence of ischemia, oxidative metabolism of glucose decreases and anaerobic glycolysis, with its end product of lactic acid, is enhanced by increased glycolytic supply. With enhanced intracellular lactic acid accumulation, brain intracellular pH (pH) decreases and is thought to lead to compromised cellular function and, in severe cases, cell death. This hypothesis is supported by experiments showing necrosis caused by intracerebral injection of lactic acid, by the greater increase in tissue lactate and decrease in tissue pH when acute hyperglycemia accompanies global incomplete ischemia, and by the greater histological injury associated with hyperglycemic ischemia. 

**Background and Purpose** We determined the effect of chronic hyperglycemia associated with diabetes on recovery of cerebral pH after global incomplete cerebral ischemia.

**Methods** 31P magnetic resonance spectra and cerebral blood flow (radiolabeled microspheres) were measured in three groups of dogs: (1) chronic hyperglycemic diabetes (pancreatectomy followed by blood glucose >10 mmol/L for 3 months; n=8); (2) acute hyperglycemia during ischemia and reperfusion in nondiabetic dogs (n=8); and (3) normoglycemic controls (n=8). Incomplete ischemia was produced for 20 minutes by ventricular fluid infusion followed by 3 hours of reperfusion.

**Results** Cerebral blood flow was reduced to approximately 5 mL/min per 100 g in all groups during ischemia with individual values ranging from 1 to 11 mL/min per 100 g. Blood flow returned to preischemic values by 30 minutes of reperfusion in the normoglycemia group but remained elevated during reperfusion in the acute hyperglycemia and diabetes groups. Cerebral pH at the end of ischemia was lower in acute hyperglycemia (5.94±0.05; ±SE) and diabetes (5.97±0.08) groups than in the normoglycemia group (6.27±0.02). However, recovery of pH through 90 minutes of reperfusion in the normoglycemia (7.08±0.05) and diabetes (7.00±0.04) groups was significantly greater than in the acute hyperglycemia group (6.74±0.11). Persistent acidosis in the acute hyperglycemia group was associated with a delayed reduction of cerebral oxygen consumption and high-energy phosphates and with greater cortical water content and impairment of somatosensory evoked potentials compared with the diabetes group.

**Conclusions** This study shows that cerebral pH recovery after global incomplete ischemia is improved in chronic hyperglycemia compared with acute hyperglycemia, despite similar decreases in blood flow and pH during ischemia and similar levels of blood flow and glucose levels during ischemia and reperfusion. In addition, cerebral pH recovery in chronic hyperglycemic dogs was not different from that in normoglycemic controls. These results suggest that an adaptation occurs with chronic hyperglycemia that improves recovery of cerebral pH during reperfusion and that is associated with better maintenance of energy metabolism and evoked potentials and with less edema over 3 hours of reperfusion compared with acute hyperglycemia. (Stroke. 1994;25:1449-1455.)

**Key Words** cerebral ischemia • diabetes mellitus • hyperglycemia • dogs

---

**See Editorial Comment, page 1455**

In these experimental studies, hyperglycemia was induced acutely before ischemia. Clinically, diabetes is associated with an increased incidence of cardiovascular morbidity and a poorer neurological outcome after stroke. While it is assumed that chronic hyperglycemia associated with diabetes adversely affects stroke outcome, the vascular pathology associated with this disease may also be important. Our laboratory has used the pancreatectomized dog model of diabetes to examine the effects of chronic hyperglycemia on cerebral blood flow (CBF) and metabolism. In this model, histologically defined microangiopathy does not occur until after 2 to 3 years of poorly controlled diabetes. Thus, by examining shorter periods of diabetes, the effects of chronic hyperglycemia before the development of microangiopathy can be assessed. Recently, Warner et al reported that 5 to 7 days of streptozocin-induced diabetes in rats without insulin treatment resulted in augmented ischemic damage.

The aim of the present study was to determine the effect of the chronic hyperglycemia of diabetes on pH during cerebral ischemia and on immediate metabolic recovery. By comparing the results in diabetic dogs with equivalent levels of acute hyperglycemia before and during ischemia and during reperfusion in nondiabetic dogs, we determined whether there are adaptations to...
chronic hyperglycemia that influence the cerebral metabolic response to global ischemia as assessed by phosphorus magnetic resonance spectroscopy (MRS). Comparisons were also made with normoglycemic controls. We tested the hypothesis that the decrease in pH during ischemia is greater with diabetic chronic hyperglycemia than with nondiabetic acute hyperglycemia and that augmented acidosis persists during reperfusion in association with persistent hyperglycemia.

Materials and Methods

All procedures were approved by the institution's animal care and use committee. To produce diabetes, total pancreatectomy under halothane anesthesia was performed on conditioned, purebred, male beagle dogs as described previously.13,14 Surgery was followed by a 3-month period of blood glucose management with subcuticular insulin injections. Daily blood samples were drawn from a foreleg vein between 8 and 9 AM (after overnight fasting) and at 3 PM (after main feeding) for analysis of glucose. The dose of insulin was adjusted individually to maintain blood glucose between 10 and 17 mmol/L throughout the day and averaged 1.4 U/kg per day.13,14

On the day of the experiment, dogs were anesthetized with fentanyl (50 µg/kg IV) and pancuronium bromide (10 mg/kg IV) followed by a pentobarbital infusion (3 mg/kg per hour IV). Pancuronium bromide (0.1 mg/kg IV) was injected for muscle paralysis. The trachea was intubated, and the lungs were mechanically ventilated. Vascular catheterization was the same as previously described. A thermistor was inserted between bone and dura to monitor epidural temperature. A Silastic ventricular drain catheter with multiple side ports was inserted into the lateral ventricle for measuring intracranial pressure (ICP) and infusing artificial cerebrospinal fluid (CSF). A silver ball electrode was secured in a burr hole over the somatosensory cortex for measuring somatosensory evoked potentials (SEPs).5 The body of the dog was wrapped in a plastic bag and placed on a blanket perfused with recirculating warm water. The head was held in a frame to maintain constant position of the MRS coil over the skull. A 5-cm layer of fiberglass insulation in a 5-cm diameter (Dupont NEN Products) as a control area under each peak. The area under the β-peak of the nucleotide triphosphate was used for adenosine triphosphate (ATP). Chemical shift (α) relative to phosphocreatine was measured, and pH, was calculated as pH,=6.73+log[(a-3.07)/ (5.68-α)]. An external standard (dimethyl 2-oxopropan phosphorurate) was used to verify spectral position when phosphocreatine disappeared. Intracellular bicarbonate concentration was calculated from the Henderson-Hasselbalch equation using a pK, of 6.12, pH, measured by MRS, and sagittal sinus PCO2 with a solubility coefficient of 0.0314 mmol/L/mm Hg.5 Changes in sagittal sinus PCO2 were assumed to approximate changes in tissue PCO2.

Three groups of dogs (n=8 each) were studied: (1) chronic hyperglycemic diabetic dogs in which fasting and afternoon blood glucose was maintained at >10 mmol/L for a duration of 3 months; (2) acute hyperglycemic nondiabetic dogs that were intravenously administered 50% dextrose approximately 20 minutes before ischemia and were maintained on a continuous infusion of 50% dextrose at a variable rate to keep blood glucose >10 mmol/L throughout ischemia and reperfusion; and (3) normoglycemic controls. To document antecedent blood glucose control in these groups, hemoglobin A1C (Sigma) was measured, and pH, was calculated as previously described. Areas under each peak were obtained as previously described. Areas under each peak were analyzed by planimetry and expressed as a percentage of the control area under each peak. The area under the β-peak of the nucleotide triphosphate was used for adenosine triphosphate (ATP). Chemical shift (α) relative to phosphocreatine was measured, and pH, was calculated as pH,=6.73+log[(a-3.07)/ (5.68-α)]. An external standard (dimethyl 2-oxopropan phosphorurate) was used to verify spectral position when phosphocreatine disappeared. Intracellular bicarbonate concentration was calculated from the Henderson-Hasselbalch equation using a pK, of 6.12, pH, measured by MRS, and sagittal sinus PCO2 with a solubility coefficient of 0.0314 mmol/L/mm Hg. Changes in sagittal sinus PCO2 were assumed to approximate changes in tissue PCO2.

Results

Before pancreatectomy, body weight was 11.8±3.9 kg. After 3 months of diabetes, there was little change in weight (+0.5±0.2 kg). The daily insulin dose was 1.4±0.1 U/kg. The morning blood glucose level before feeding was 11.5±0.6 mmol/L with a daily coefficient of variation in individual dogs averaging 31% over the 3-month period. The afternoon blood glucose level after the main feeding was 13.7±0.7 with a daily coefficient of variation of 29%. These results are similar to previous values obtained in diabetic dogs.13,14

Arterial blood analysis obtained in the three groups during ischemia and reperfusion are shown in the Table. Arterial blood gases were similar among groups. Arterial blood glucose levels in the acute hyperglycemic and diabetic dogs were similar during ischemia and reperfusion and were significantly greater than in the normoglycemic group. Hemoglobin A1C levels were significantly elevated after 3 months of low-dose insulin management.
(7.8±0.3%, 8.2±0.7%, and 11.9±0.5% hemoglobin A1C in normoglycemia, acute hyperglycemia, and diabetes groups, respectively). These elevations occurred without increases in blood ketone levels (0.7±0.2, 0.6±0.0, 1.0±0.1 mmol/L β-hydroxybutyrate in normoglycemia, acute hyperglycemia, and diabetes groups, respectively).

With elevation of ICP, mean arterial pressure initially increased over the first 7 minutes of ischemia and then returned toward baseline as ischemia continued (Fig 1). As this occurred, ICP was adjusted to maintain cerebral perfusion pressure at 10 mm Hg. In all three groups, mean arterial pressure did not differ significantly from baseline after 7 minutes of ischemia or throughout the reperfusion period. Intracranial pressure returned to baseline as ischemia continued (Fig 1).

Preischemic CBF was similar in all three groups. Blood flow to cerebral cortex was reduced to 5 mL/min per 100 g during ischemia (Fig 2) with individual values ranging from 1 to 11 mL/min per 100 g. Hyperemia at 7 minutes of reperfusion was similar among groups. Blood flow returned to preischemic values by 30 minutes of reperfusion in the acute hyperglycemia group but persisted through 90 minutes of reperfusion in the acute hyperglycemia and diabetes groups. Delayed hypoperfusion was detected at 90 and 180 minutes in the normoglycemia group but was not observed in acute hyperglycemia and diabetes groups. Regional CBF in subcortical regions, brain stem, and cerebellum showed a similar pattern to that in cerebral cortex within each group.

During ischemia, CMRO2 was markedly reduced (Fig 2). In the normoglycemia and diabetes groups, recovery of CMRO2 was sustained throughout reperfusion, whereas significant reductions occurred in the acute hyperglycemia group at 90 and 180 minutes of reperfusion.

End-ischemic pH was lower in acute hyperglycemia (5.94±0.05) and diabetes groups (5.97±0.08) than that obtained in the normoglycemia group (6.27±0.02). The level of ischemic acidosis was similar in diabetes and acute hyperglycemia groups. However, recovery of pH in the diabetes group was similar to that in the normoglycemia group and significantly greater than that in the acute hyperglycemia group (Fig 3). Estimated intracellular bicarbonate ion concentration fell sharply during ischemia in all groups (Fig 3). During reperfusion, bicarbonate recovered in the normoglycemia and diabetes groups, whereas in the acute hyperglycemia group bicarbonate remained depressed throughout reperfusion.

There was no significant difference in the level of ATP attained at the end of ischemia among the normoglycemia (32±13% of baseline), acute hyperglycemia (30±13%), and diabetes (56±13%) groups. There was also no difference among groups in ATP recovery (Fig 4). However, in the acute hyperglycemia group, there was a secondary decrease of ATP to 58±13% of baseline at 180 minutes of reperfusion. End-ischemic phosphocreatine was greater in the diabetes group (28±5% of baseline) than in the normoglycemia (14±6%) and acute hyperglycemia (2±2%) groups. In the normoglycemia and diabetes groups, phosphocreatine returned

### Analysis of Arterial Blood

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Ischemia, 12 Min</th>
<th>7 Min</th>
<th>30 Min</th>
<th>90 Min</th>
<th>180 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>3.2±0.2</td>
<td>5.2±0.5</td>
<td>5.5±0.5</td>
<td>3.9±0.3</td>
<td>3.3±0.3</td>
<td>3.2±0.2</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>4.0±0.4</td>
<td>17.9±1.6*</td>
<td>17.5±1.8</td>
<td>16.4±1.2</td>
<td>14.5±1.4</td>
<td>16.1±1.2*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.0±1.3*</td>
<td>17.4±1.5*</td>
<td>17.6±1.6</td>
<td>16.7±1.5</td>
<td>16.1±1.3</td>
<td>15.5±1.2*</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>7.40±0.1</td>
<td>7.36±0.01</td>
<td>7.32±0.01</td>
<td>7.32±0.01</td>
<td>7.36±0.01</td>
<td>7.35±0.01</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>7.38±0.1</td>
<td>7.32±0.01*</td>
<td>7.29±0.01*</td>
<td>7.28±0.01*</td>
<td>7.34±0.01</td>
<td>7.34±0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.39±0.1</td>
<td>7.38±0.01</td>
<td>7.34±0.01</td>
<td>7.34±0.01</td>
<td>7.37±0.01</td>
<td>7.36±0.01</td>
</tr>
<tr>
<td>Pco2, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>38±1</td>
<td>38±1</td>
<td>38±1</td>
<td>37±1</td>
<td>38±1</td>
<td>36±1</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>38±1</td>
<td>39±1</td>
<td>40±1</td>
<td>38±0</td>
<td>38±1</td>
<td>37±1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39±0</td>
<td>37±1</td>
<td>38±1</td>
<td>38±1</td>
<td>37±0</td>
<td>37±1</td>
</tr>
<tr>
<td>Po2, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>144±7</td>
<td>145±5</td>
<td>143±6</td>
<td>140±9</td>
<td>136±9</td>
<td>137±9</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>145±7</td>
<td>136±8</td>
<td>139±6</td>
<td>140±9</td>
<td>152±9</td>
<td>159±5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>137±4</td>
<td>131±5</td>
<td>132±5</td>
<td>136±5</td>
<td>138±4</td>
<td>132±5</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>15.7±0.7</td>
<td>17.6±0.5</td>
<td>16.8±0.7</td>
<td>16.4±0.9</td>
<td>15.5±0.7</td>
<td>14.8±0.7</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>15.5±1.0</td>
<td>16.2±0.8</td>
<td>15.0±0.9</td>
<td>14.9±0.9</td>
<td>13.5±1.1</td>
<td>13.5±1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.1±0.5</td>
<td>16.1±0.3</td>
<td>15.6±0.4</td>
<td>14.8±0.4</td>
<td>14.6±0.6</td>
<td>14.0±0.6</td>
</tr>
</tbody>
</table>

Values are mean±SE. *P<.05 from normoglycemia group at respective time.
This study shows that pH, recovery after global incomplete ischemia was better in chronic hyperglycemia than acute hyperglycemia, despite similar decreases in pH, and CBF during ischemia and despite similar elevation of blood glucose level during ischemia and reperfusion. In addition, pH, recovery in chronic hyperglycemia was not different from recovery in normoglycemic controls. These results indicate that acute hyperglycemia initiated just before ischemia and maintained throughout reperfusion worsens pH,, whereas chronic hyperglycemia of 3 months’ duration does not worsen pH, and metabolic recovery. This suggests that an adaptation occurs with chronic hyperglycemia that improves recovery of pH, during reperfusion. Furthermore, these results indicate that chronic hyperglycemia without superimposed microangiopathy causes changes in the ability of the brain to regulate pH, after ischemia.

There are several adaptations to chronic hyperglycemia that may cause the diabetic subject to respond differently to cerebral ischemia. First, the ketonemia that occurs with diabetes may have a protective effect during hypoxic episodes. However, the ketone levels in our diabetic dogs were not elevated from those of nondiabetic dogs. Second, insulin can modulate ischemic brain damage. In the present study, the diabetic dogs received no insulin for at least 24 hours before the experiment. Therefore, higher insulin levels could not account for improved recovery in the diabetic dogs. Third, diabetes leads to increased activity of the polyol pathways and protein kinase C, changes which are thought to inhibit the activity of Na⁺,K⁺-ATPase. Such inhibition could conserve phosphocreatine and ATP during ischemia. The slightly higher end-ischemic
phosphocreatine in the diabetes group (28±5% of baseline) than in the acute hyperglycemia group (2±2%) supports this hypothesis. Less depletion of phosphocreatine during ischemia theoretically could accelerate pH recovery by providing greater energy reserves at the onset of reperfusion. Fourth, carbohydrate stores at the onset of ischemia may be higher in the diabetes group. With the reported 40% elevation in brain glycogen content as measured in diabetic rats, it is possible that cerebral high-energy phosphates could be better maintained for several minutes. However, it is unlikely that elevated glycogen could sustain phosphocreatine for 20 minutes with the severity of ischemia produced in the present study, unless there was also a concurrent reduction in energy demand.

It is clear that the augmented lactic acid production by hyperglycemia contributes to brain acidosis. As in previous reports, the present study found delayed reductions in CMRO₂ and high-energy phosphates in the acute hyperglycemia group accompanied by greater depression of SEPs and greater edema formation. However, the present study differs from previous studies in that elevated glucose was maintained throughout reperfusion. Persistent hyperglycemia after an ischemic insult may have contributed to the persistent acidosis in this group and accelerated the delayed metabolic alterations. In support of this possibility, persistent acidosis during reperfusion has been found to cause additional depression of postischemic SEPs. Furthermore, Siemkowicz found that combined preischemic plus postischemic hyperglycemia produced greater neurological deficit than preischemic hyperglycemia alone. Thus, the early improvement in pH recovery seen in the diabetes group may be important in preventing delayed metabolic deterioration.

The role of persistent lactic acid production in determining pH recovery during reperfusion is unclear. Widmer et al noted persistent lactate levels in postischemia only in rats with extremely high glucose levels. Persistent lactic acidosis depends on two separate effects: (1) lactic acid production that is dependent on rate of glucose consumption relative to restoration of oxidative phosphorylation and (2) rate of lactic acid efflux. The rate of brain glucose influx and lactic acid production during reperfusion may be higher in acute hyperglycemia than diabetes and account for the slower pH recovery in acute hyperglycemia. Lactate was not measured in this study to discern this possibility. Recovery of pH may also depend on lactate transport across cell membranes and across the blood-brain barrier.
barrier via the monocarboxylic carrier-mediated transport system.33 Diabetes can increase blood-brain barrier transport of butyrate,24 which uses the monocarboxylic carrier. Thus it is possible that diabetes increases blood-brain barrier efflux of lactate during reperfusion and thereby accelerates pH recovery.

It is controversial whether blood-brain glucose transport is altered in diabetes. Some investigators report that the number of brain glucose transporters following streptozotocin-induced diabetes is decreased,35 and other data suggest that maximum glucose transport capacity of the blood-brain barrier is decreased.36 However, these results could not be verified by other investigators, who in fact have reported an increase in microvessel transporter density.37,38 Changes in transporter density could influence the level of tissue lactic acidosis during ischemia and reperfusion. One might expect that a change in glucose transporter density would have an impact on glucose uptake when blood flow is low. However, we did not detect any difference in ischemic pH between acute hyperglycemia and diabetes groups, suggesting that any differences in transporter density were not of sufficient magnitude to have an impact on the degree of lactic acidosis during ischemia.

Three concerns must be expressed as to the clinical relevance of this study. First, the method of production of acute hyperglycemia, namely the continuous infusion of 50% dextrose, does not accurately represent the acute hyperglycemia of human stroke, which is a stress response. Thus, the acute hyperglycemia of stroke patients may include more than just a simple elevation of glucose and also involve glucocorticoids. The conclusions regarding acute hyperglycemia in this study may not be applicable to the acute hyperglycemia in nondiabetic stroke patients. Our rationale for inclusion of an acute hyperglycemia group was merely to act as a control for the known adverse effects of elevated glucose during global ischemia. Second, our data are limited to 3 hours of reperfusion. Warner et al16 showed that diabetic rats without insulin treatment had greater ischemic neuronal injury than normoglycemic rats. Thus, we cannot exclude that delayed neuronal necrosis would be greater in dogs with uncontrolled diabetes. On the other hand, delayed postischemic pH recovery in acute hyperglycemia is associated with greater histopathologic damage.1,5,9,10 Third, these results may be specific for conditions of this experiment, namely, (1) 3 months' duration of diabetes, (2) global and not focal ischemia, (3) severe incomplete ischemia and not necessarily complete ischemia, and (4) 20-minute ischemia duration.

In summary, this study shows that chronic hyperglycemia associated with diabetes causes adaptations in the brain that hasten the recovery of pH, after ischemia and result in better maintenance of energy metabolism, SEPs, and tissue water content compared with acute hyperglycemia. Possible adaptations include alterations in blood-brain barrier transport of glucose and lactate or reduced energy demand during the ischemic period.

Acknowledgments

This study was supported by US Public Health Service National Institutes of Health grant NS-01380. The authors thank Ying Wu, Judy Klaus, and Kathleen Blizzard for their tireless technical assistance and Lee Palmer for her help in preparing this manuscript.

References


Downloaded from http://stroke.ahajournals.org/ by guest on April 13, 2017
Despite significant recent attention to the sequelae of hyperglycemia in cerebral ischemia in both the clinical and basic science literature, no definite recommendations can be made on glucose management in the acute stroke patient. Further understanding of the effects (and the mechanisms of these effects) of hyperglycemia on infarcted brain tissue in the setting of diabetes and that of stress-induced hyperglycemia is needed.

Sieber et al have added some interesting and surprising observations in this area by comparing multiple physiological parameters, notably energy metabolism and the duration of acidosis in dogs with incomplete transient global cerebral ischemia with (1) diabetes and chronic hyperglycemia, (2) acute hyperglycemia induced by glucose infusion, and (3) normoglycemic controls. The finding of longer reduction of energy metabolism and more prolonged acidosis in the nondiabetic hyperglycemic animals as compared with the diabetic animals is unexpected and is used by the authors to suggest that adaptive processes take place over time in hyperglycemic diabetic animals. High insulin levels, which can modulate ischemic brain damage, were not considered a factor because the diabetic dogs had not received insulin for 24 hours. It should be noted that the nondiabetic animals, which likely had very high insulin levels in response to hyperglycemia, would be the group most likely to have been protected by this mechanism, yet this is the group with the worst outcome.

It would be interesting to see a comparison between diabetic hyperglycemic animals and nondiabetic animals with glucocorticoid-induced hyperglycemia (more likely to mimic the stress hyperglycemia seen in some stroke patients). The study of diabetic animals with chronically tight control of diabetes but with acute hyperglycemia after cerebral ischemia, to determine whether chronic hyperglycemia or some other factor in the diabetic animals improved the metabolic outcome, would also be interesting. It also would be important to study the same phenomena in models of focal cerebral ischemia, which more closely mimic human stroke.

The follow-up studies, including those that may explain the apparent adaptive factors to hyperglycemia in diabetic animals, will be awaited with interest.

Nancy Futrell, MD, Guest Editor
Department of Neurology
Creighton University
Omaha, Neb

References

Diabetic chronic hyperglycemia and cerebral pH recovery following global ischemia in dogs.
F E Sieber, R C Koehler, P R Brown, S M Eleff and R J Traystman

Stroke. 1994;25:1449-1455
doi: 10.1161/01.STR.25.7.1449
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/25/7/1449

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/