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# Hyperglycemia Augments Ischemic Brain Injury: In Vivo MR Imaging/Spectroscopic Study with Nicardipine in Cats with Occluded Middle Cerebral Arteries

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Hyperglycemia is often associated with an increased frequency of cerebrovascular disease and exacerbation of neuronal injury in focal ischemic cerebral infarction. We used a combination of high-field proton MR imaging and <sup>1</sup>H and <sup>31</sup>P MR spectroscopy to investigate whether hyperglycemia would adversely influence cerebral metabolism and eventual infarct size following unilateral occlusion of the middle cerebral artery (MCA) of cats pretreated with the calcium channel blocker nicardipine. Normoglycemic animals injected with 10 μg/kg of nicardipine (8 μg·kg<sup>-1</sup>·hr<sup>-1</sup> maintenance dose) manifested only mild disturbances in phosphorus metabolism and cerebral pH regulation compared with untreated controls, and showed a significant reduction in infarct size 7 hr after MCA occlusion. By comparison, hyperglycemic cats (plasma glucose, 200–300 mg/dl) had significantly reduced cerebral high-energy phosphates, elevated lactic acid, and larger ischemic lesions in the occluded MCA territory, irrespective of whether they were treated with nicardipine.

These results indicate that moderate hyperglycemia can exaggerate ischemic brain damage by enhancing formation of tissue lactic acid and impairing normal phosphorus metabolism. One implication of this study is that dextrose should not be provided to patients with acute ischemic stroke.

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Hyperglycemia is one of the factors that can accentuate brain damage induced by acute cerebral ischemia. Investigations in experimental animals with controlled preischemic feeding or glucose infusion have demonstrated that hyperglycemia can severely aggravate stroke-induced brain edema and disrupt cerebral metabolism [1–3]. Increased damage after ischemic stroke has also been shown in patients with hyperglycemia, with or without established diabetes mellitus [4].

Calcium influx into ischemically injured neurons is also known to adversely affect membrane ion transport and cell energetics [5, 6]. Calcium channel blockers appear to inhibit calcium entry into injured neurons and prevent or reduce metabolic disturbances associated with ischemia [7–9]. In the present study, we evaluated the effects of administering a specific calcium channel entry blocker, nicardipine, on cerebral edema, phosphorus metabolism, and lactate accumulation in moderately hyperglycemic and normoglycemic cats subjected to acute regional cerebral ischemia. Nicardipine has previously been shown to significantly reduce brain infarct size and preserve cerebral high-energy phosphates following permanent middle cerebral artery (MCA) occlusion in cats [10].

Proton MR imaging was used to detect alterations in brain tissue water content in normoglycemic and hyperglycemic nicardipine-treated and untreated MCA-occluded cats. <sup>31</sup>P and <sup>1</sup>H MR spectroscopic studies were performed concurrently to compare the extent of cerebral metabolic injury. Histochemical mapping of the viability of brain tissues was carried out by using 2,3,5-triphenyltetrazolium chloride (TTC) [11, 12] in order to spatially correlate the evolution of ischemic tissue injury with the MR imaging/spectroscopic results 5–9 hr after MCA occlusion.

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## Materials and Methods

All procedures involving animals followed the National Institutes of Health guidelines and were given prior approval by the University of California, San Francisco, Committee on Animal Research.

Cats of either sex weighing 2–5 kg were anesthetized with sodium pentobarbital (30–35 mg/kg IV). An endotracheal tube was inserted, and the animals were ventilated with a respirator (North American Drager) to maintain normal oxygen (100–120 mm Hg) and carbon dioxide (32–38 mm Hg) tensions. A femoral vein and artery were cannulated with polyethylene catheters for continuous blood pressure monitoring and drug and glucose administration, respectively. Arterial blood gases, pH, and plasma glucose concentrations were measured at 1 to 2 hr intervals beginning 1 hr before the induction of stroke. The rectal temperature was maintained at  $37 \pm 0.5^\circ\text{C}$  by using an electronically controlled body heating pad. Isotonic sodium chloride fluids were administered throughout the surgical procedure.

The cat's head was immobilized in a stereotaxic device. The right orbit was exenterated and the optic foramen and orbital fissure were enlarged with a dental drill to expose the dura overlying the origin of the right MCA from the internal carotid artery. The arachnoid was dissected by using an operating microscope, and the MCA was occluded just proximal to the origin of the lateral striate arteries with bipolar electrocautery. The MCA was then completely transected, and the dural incision and orbit were covered with saline-moistened gauze or Gelfoam. The temporal muscles ipsilateral to the MCA occlusion were excised to optimize the external placement of the surface coil over the MCA territory in the parietal and frontal cortices. The cat was then immediately placed in the MR imaging/spectroscopic unit.

### MR Imaging

Coronal and axial brain images were obtained by using a General Electric CSI-II spectrometer/imager operating at 2.0 T. A home-built "bird cage" resonator head coil with an inner diameter of 8.3 cm was tuned to the proton resonant frequency of 85.552 MHz and used to acquire two-dimensional spin-echo images. Other machine parameters included an 8- by 8-cm field of view, a 5-mm-thick slice, and an acquisition matrix of 128 phase-encoded steps by 256 complex frequency-encoding points. Two spin-echo sequences were used: a four-slice T2-weighted sequence, 3000/100 (TR/TE), with two acquisitions and a single-slice T1-weighted sequence. Region-of-interest MR intensity measurements were carried out in the injured parietal and temporal cortices, internal capsule, caudate nucleus, and corresponding uninjured contralateral regions in drug-treated and control animals.

### MR Spectroscopy

Spectra were obtained by using a circular 1.5-cm two-turn balance-matched surface coil tuned to the phosphorus (34.631 MHz) or proton (85.58 MHz) resonant frequency, and fixed with adhesive directly to the skull surface overlying the cortex in the distribution territory of the occluded MCA. The surface coil was centered in a standard position 1.0 cm lateral and 0.8 cm posterior to the bregma. A simple presaturation one-pulse excitation-acquisition experiment with an interpulse delay of 2000 msec and 256 acquisitions allowed a  $^{31}\text{P}$  spectrum to be acquired every 10 min. The bone phosphorus signal was saturated with a low-power presaturation pulse of 1000 msec.

Spectral enhancement (gaussian line broadening of 15 Hz) was used to display the spectra. Spectra were phased and deconvoluted. Individual resonances were then subjected to an iterative line-fitting simulation computer program by using a least-squares fit algorithm.

The beta-, alpha-, and gamma-adenosine triphosphate (ATP); phosphocreatine; phosphodiester; inorganic phosphate; and phosphomonoester peaks were identified (Fig. 1) with the investigator blinded to the experimental condition of each animal. From these areas, the inorganic phosphate/phosphocreatine (Pi/PCr) ratio was calculated in order to quantify the bioenergetic status of the tissues. Intracellular pH was calculated from the chemical-shift difference (delta) between the  $^{31}\text{P}$  signals of inorganic phosphate and phosphocreatine by using the titration curve,

$$\text{pH} = 6.77 + \log_{10} \left[ \frac{(\text{delta} - 3.29)}{(5.68 - \text{delta})} \right]$$

$^1\text{H}$  MR spectra showed an *N*-acetylaspartate (NAA) peak at 2.0 ppm before MCA occlusion, and an increasing lactate peak at 1.3 ppm following stroke. The lactate  $\text{CH}_3$  peak could be distinguished from the residual lipid signal also present at 1.3 ppm by selectively inverting the lactate CH protons.

### Experimental Protocol

The animals were assigned to one of four experimental groups: normoglycemic (plasma glucose, 80–120 mg/dl;  $n = 9$ ); normoglycemic with nicardipine pretreatment ( $n = 8$ ); hyperglycemic (plasma glucose, 200–300 mg/dl;  $n = 5$ ); and hyperglycemic with nicardipine pretreatment ( $n = 5$ ). Animals in both hyperglycemic groups were not fasted overnight prior to the experiment, and were given IV infusions of 25% D-glucose to keep glucose levels between 200 and 300 mg/dl (11–17 mmol/l) throughout the 5- to 9-hr study period. Nicardipine (Cardene, Syntex Laboratories, Palo Alto, CA) was administered initially as a  $10 \mu\text{g}/\text{kg}$  IV injection 15 min prior to MCA occlusion. After the initial bolus IV injection, nicardipine was maintained at a maintenance dose of  $8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$  IV for the 5- to 7-hr duration of each experiment. The first MR spectrum was obtained within 30 min after MCA occlusion, and MR imaging/spectroscopic studies were performed sequentially at 30–55 min, 120–145 min, and 270–315 min after occlusion. Mean arterial blood pressure and heart rate were monitored continuously throughout the MR experiments.

At the conclusion of each MR imaging/spectroscopic study, the animals were removed from the magnet and given a supplemental

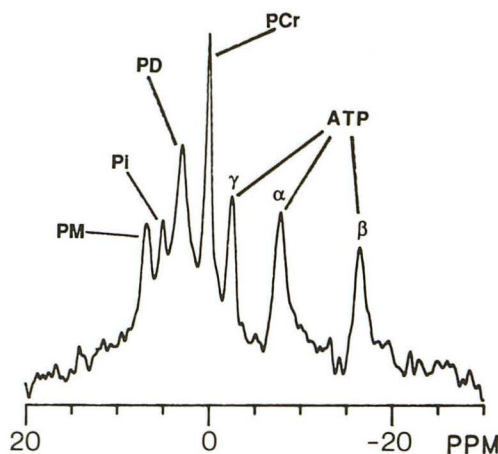


Fig. 1.—Normal  $^{31}\text{P}$  MR spectrum obtained from a surface coil positioned over middle cerebral artery vascular territory. Individual phosphorus resonances are phosphomonoesters (PM); inorganic phosphate (Pi); phosphodiester (PD); phosphocreatine (PCr); and gamma, alpha, and beta adenosine triphosphate (ATP).

dose of IV sodium pentobarbital to induce deep surgical anesthesia. Forty to sixty milliliters of a 2% solution of TTC was immediately injected into the ascending aorta. Tetrazolium salts are widely used as indicators for the histochemical determination of dehydrogenases [11]. When TTC is incubated in the dark with normal brain tissue it is reduced to a red formazan-insoluble product that is deposited on the brain surface [12]. This reaction requires the integrity of the intracellular cycle of the reduced form of nicotinamide adenine dinucleotide. Normal brain tissues stain red while injured brain tissues stain pink (ischemic) and gray/white (necrotic).

The brain was removed from the calvaria 20 min after perfusion with TTC and then immersed in 2% TTC for approximately 20 min. The brain was then placed in 10% buffered formalin for 16–24 hr. Subsequently, 3-mm-thick coronal sections were cut, starting at the midcollicular level and proceeding anteriorly. The sections were photographed by using color slide film, and the projected slides were analyzed by using a planimeter to estimate the area of ischemic/infarcted tissue in the control and nicardipine-treated groups.

#### Statistical Analysis

Quantitative data are expressed as means  $\pm$  SEM. For comparisons between the control and nicardipine-treated groups, the unpaired Student's *t* test was used. For comparisons of cerebral tissues ipsilateral and contralateral to the MCA occlusion, the paired Student's *t* test was used. A probability of .05 or less was considered to be statistically significant.

#### Results

Within 30 min of MCA occlusion there was a clear increase in the inorganic phosphate signal in both normoglycemic and hyperglycemic cats not pretreated with nicardipine. The inorganic phosphate of injured tissue split from the inorganic phosphate of normal tissue and shifted toward the phosphodiester peak, reflecting a progressive drop in intracellular pH during the 5-hr period of ischemia. The magnitude of these changes in intracellular pH is in general agreement with previous MR spectroscopic studies in MCA-occluded cats in which the intracellular pH was measured with a surface coil [10, 13], or topographically with the use of neutral red as an internal pH indicator [14].

Substantial qualitative and quantitative differences in brain phosphorus metabolism were observed in the four groups of animals (Table 1). Pretreatment with nicardipine preserved a low Pi/PCr ratio in normoglycemic cats compared with untreated control animals. In hyperglycemic nicardipine-treated cats, however, the Pi/PCr ratio was maintained near preischemic levels for 2 hr after occlusion, but by 5 hr after occlusion the mean Pi/PCr ratio had increased considerably, and was not significantly different from that of untreated controls. Moreover, in hyperglycemic animals, cerebral intracellular pH in the vascular territory of the occluded MCA was lower at 2 hr after occlusion than in nicardipine-treated and untreated controls. Hyperglycemic MCA-occluded cats also became progressively more acidotic than normoglycemic drug-treated animals and normoglycemic untreated controls. Owing to the variable responses of individual cats in both the treated and control groups, the averaged quantitative differences were not statistically significant. The 1.5-cm coil was

**TABLE 1: Averaged Inorganic Phosphate/Phosphocreatine (Pi/PCr) Ratios and Intracellular pH Under Normo- and Hyperglycemic Conditions 2 and 5 hr After Unilateral Occlusion of the Middle Cerebral Artery in Cats with and Without Nicardipine Pretreatment**

Group	Pi/PCr Ratio		Intracellular pH	
	2 hr	5 hr	2 hr	5 hr
Normoglycemic				
Not pretreated ( <i>n</i> = 9)	1.34 $\pm$ 0.52	1.39 $\pm$ 0.89	7.04 $\pm$ 0.18	6.85 $\pm$ 0.12
Pretreated ( <i>n</i> = 8)	0.43 $\pm$ 0.31	0.44 $\pm$ 0.37	7.24 $\pm$ 0.15	7.18 $\pm$ 0.23
Hyperglycemic				
Not pretreated ( <i>n</i> = 5)	0.94 $\pm$ 0.60	1.20 $\pm$ 0.48	6.71 $\pm$ 0.24	6.67 $\pm$ 0.22
Pretreated ( <i>n</i> = 5)	0.92 $\pm$ 0.31	1.34 $\pm$ 0.38	6.83 $\pm$ 0.19	6.66 $\pm$ 0.21

Note.—Values are means  $\pm$  SEM. Plasma glucose levels in normoglycemic cats were maintained at 80–120 mg/dl; levels in hyperglycemic cats were maintained at 200–300 mg/dl.

placed in a standard location over the MCA territory, so that most of the signal originated from brain tissues within approximately 8 mm of the surface [10]. It seems likely, however, that signal was obtained from both the ischemic focus and the surrounding, variably less injured penumbra. Using the same MCA occlusion model of regional cerebral ischemia in the cat, previous investigators also found similar heterogeneity in neurologic damage [13].

<sup>31</sup>P spectra obtained from normo- and hyperglycemic cats after MCA occlusion are shown in Figure 2. In a previous study [10] that used the same MR parameters and surgical procedure, we reported that the mean phosphocreatine/ $\beta$ -ATP ratio in fully relaxed spectra prior to arterial occlusion was 1.8  $\pm$  0.2 and the Pi/PCr ratio was 0.32  $\pm$  0.11. The average chemical shift of the inorganic phosphate resonance with respect to phosphocreatine was 4.93  $\pm$  0.13 ppm, corresponding to an intracellular pH of 7.11  $\pm$  0.11.

Prior to MCA occlusion, <sup>1</sup>H MR spectra showed a single NAA peak at 2.0 ppm, without any visible lactate peak. Within 15–60 min after MCA occlusion, a lactate peak at 1.3 ppm was also visible (Fig. 3). The lactate peak grew progressively in amplitude throughout the period of occlusion in both the drug-treated and untreated hyperglycemic animals, although the NAA/lactate ratio dropped more slowly in nicardipine-treated cats. By comparison, brain lactate levels in normoglycemic nicardipine-treated animals remained low throughout the postocclusion period.

The influence of blood glucose level on ischemic tissue damage was evaluated on MR images by comparing the total area of tissue hyperintensity on T2-weighted images after stroke was induced. In normoglycemic MCA-occluded animals without nicardipine pretreatment, high signal intensity was observed within 2 hr in the dorsolateral frontal and parietal cortices, the medial aspect of the head of the caudate, the lateral part of the globus pallidus, and most of the internal capsule and temporal lobe (Fig. 4A). Pretreatment with nicardipine produced a 71  $\pm$  19% reduction in the size of the cerebral infarct when evaluated 7 hr after MCA occlusion (Fig. 4B). By comparison, nicardipine pretreatment in hyperglycemic animals failed to significantly reduce infarct size (6  $\pm$  22%) (Fig. 5). As the data suggest, hyperglycemia may exacerbate injury in this group of animals, even with nicardipine

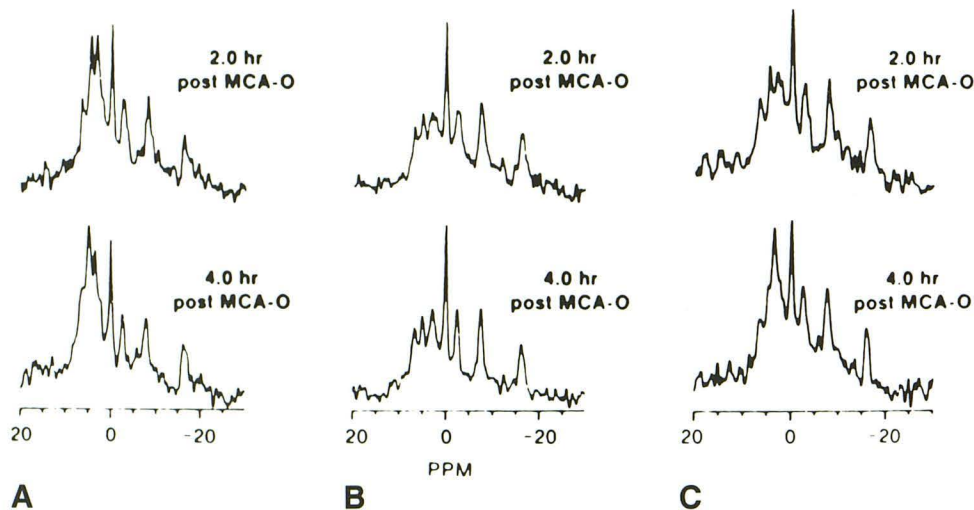


Fig. 2.—A–C,  $^{31}\text{P}$  spectra 2 and 4 hr after occlusion of the middle cerebral artery (post MCA-O) obtained with a surface coil positioned over occluded MCA vascular territory in a normoglycemic control (untreated) cat (A), a normoglycemic nicardipine-pretreated cat (B), and a hyperglycemic nicardipine-pretreated cat (C). Pretreatment with calcium antagonist preserved a low inorganic phosphate/phosphocreatine (Pi/PCr) ratio. In hyperglycemic cats, the drug failed to maintain Pi/PCr ratio near preischemic levels or stabilize intracellular pH in MCA territory.

pretreatment. Overall, there was close correspondence between the areas of hyperintensity observed on T2-weighted images 7 hr after occlusion and the distribution of infarcted tissues observed in subsequent TTC-stained sections (Figs. 4C, 4D, 5C, and 5D).

### Discussion

The results of this investigation indicate that combined MR imaging/spectroscopy is a sensitive method for the *in vivo* evaluation of drugs influencing cerebral metabolism. Unlike

subacute and chronic brain infarction, in which only minor alterations in phosphorus metabolite ratios have been found [15], acute stroke is associated with early-onset reciprocal changes in phosphocreatine and inorganic phosphate (decreased PCr/Pi ratio) and a decrease in intracellular pH [10, 15]. The disruption in high-energy phosphate production inhibits the ATP-dependent sodium-potassium transmembrane pump and causes sodium and water to accumulate intracellularly.  $^{31}\text{P}$  and  $^1\text{H}$  MR spectroscopy was applied to observing dynamic changes in the energy state of control and nicardipine-treated ischemic cat brain under normo- and hyperglycemic conditions. Concurrently, proton MR imaging was used to monitor the progress of the developing infarct. We have found in a recently completed study (Kucharczyk et al., unpublished data) that the interanimal variability in infarct size following unilateral MCA occlusion is less than 8%, if the MCA is occluded just proximal to the origin of the lenticulostriate arteries.

MR spectroscopy was able to detect changes in cerebral energy metabolism within 2–30 min after MCA occlusion, and the results in most cases accurately forecast tissue structural changes seen 60–90 min later on T2-weighted spin-echo MR images. Detection of metabolic disruption by MR spectroscopy is especially important because at this early stage of cytotoxic edema, the increase in mobile protons in the region of tissue injury is not reliably visualized on T2-weighted MR images.

We have reported previously [10] that nicardipine, a 1,4-dihydropyridine calcium channel blocker [16], can ameliorate the effects of postischemic hypoperfusion if administered 15 min before or after occlusion of the MCA. In the current study, normoglycemic animals pretreated with nicardipine manifested only mild disturbances in phosphorus metabolism and intracellular pH, compared with a progressive acidosis observed within the ischemic MCA territory of untreated normoglycemic or hyperglycemic controls. Normoglycemic cats pretreated with nicardipine also showed a reduction in cerebral infarct size 5–7 hr after MCA occlusion compared with untreated controls. These results are consistent with previous reports of the beneficial effects of calcium channel blockers

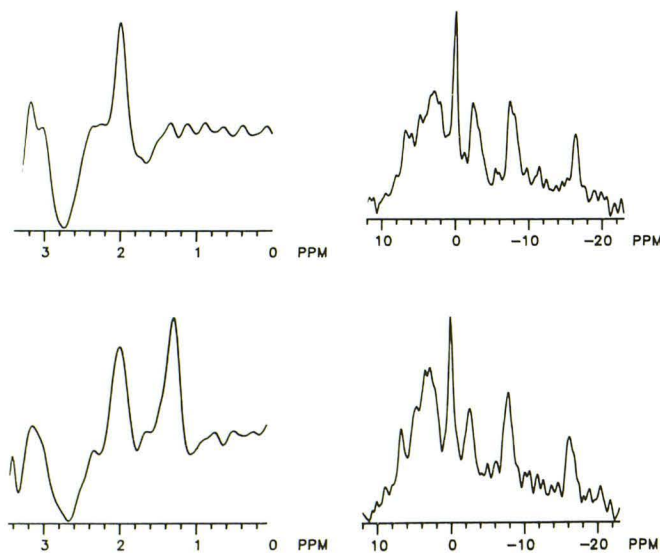


Fig. 3.— $^1\text{H}$  (left panels) and  $^{31}\text{P}$  (right panels) MR spectra obtained by using a double-tuned surface coil positioned over an occluded middle cerebral artery (MCA) vascular territory in two cats pretreated with calcium channel blocker.

A, Normoglycemic animal. Little lactate (1.3 ppm) was detected 15 min after MCA occlusion. At 30 min, inorganic phosphate/phosphocreatine (Pi/PCr) ratio was only slightly increased from preischemic levels. This animal sustained minimal brain damage, as shown in Figs. 4B and 4D.

B, When hyperglycemia was induced prior to MCA occlusion, lactate peak (1.3 ppm) and Pi/PCr were significantly elevated during immediate postocclusion period, and a large infarct was found (Figs. 5B and 5D).

Fig. 4.—A and B, T2-weighted coronal MR images at level of optic chiasm 7 hr after unilateral occlusion of middle cerebral artery in untreated (A) and nicardipine-pretreated (B) normoglycemic cats. Area of high signal intensity (arrows) indicating edema is more extensive in untreated brain (37%) compared with treated brain (14%), and extends throughout much of cortical gray matter and basal ganglia.

C and D, Coronal brain sections stained with triphenyltetrazolium chloride from animals in A and B, respectively. Normal gray matter appears black to dark gray, ischemic zones are light gray, and totally ischemic or infarcted tissues (which lack viable electron transport chain enzymes) appear white. Tissue injury (arrows) is more extensive in untreated brain (36% of coronal area) than in drug-treated brain (18% of coronal area).

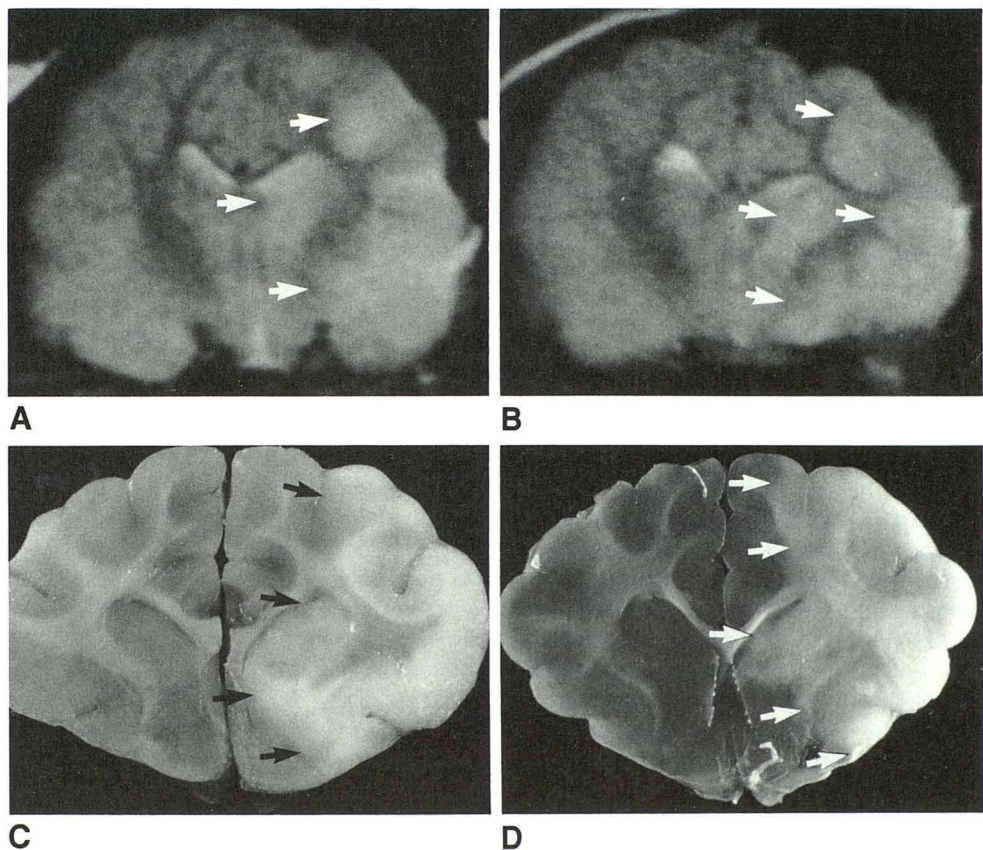
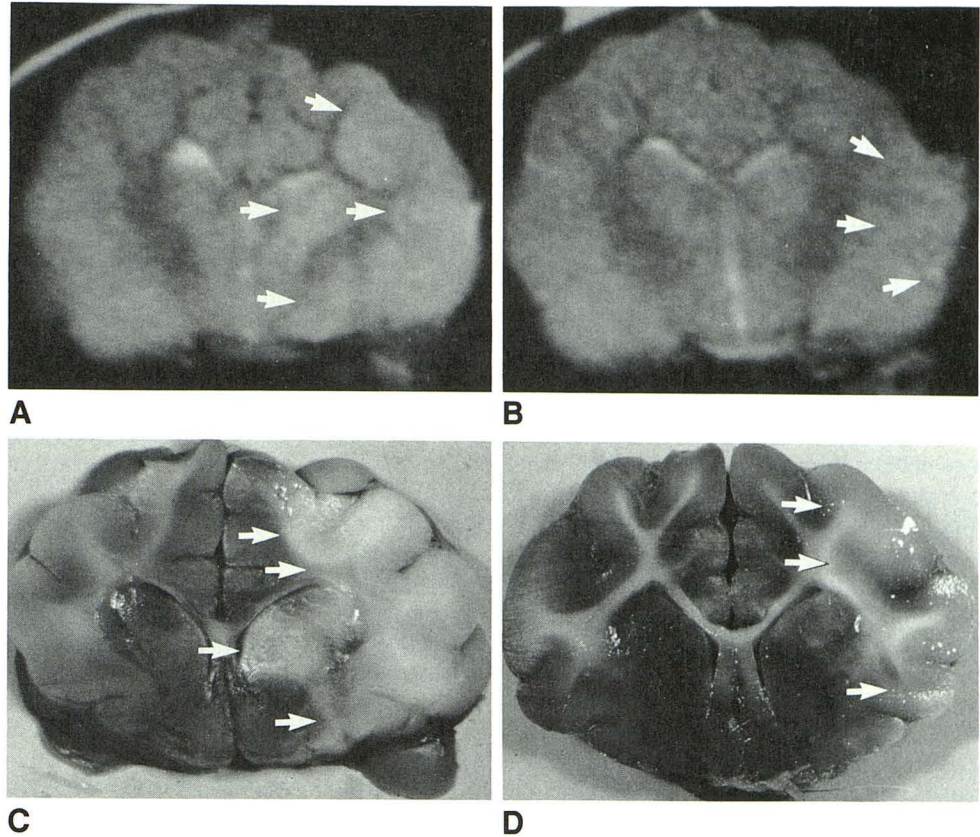


Fig. 5.—A and B, T2-weighted coronal MR images 7 hr after unilateral occlusion of middle cerebral artery (MCA) in untreated (A) and nicardipine-pretreated (B) hyperglycemic cats. High signal intensity (arrows) can be seen throughout MCA territory of both brains (34% of hemisphere in pretreated brain and 36% of untreated brain).

C and D, Coronal brain sections stained with triphenyltetrazolium chloride from animals in A and B, respectively. Tissue injury (arrows) is particularly severe in cortex of MCA territory in both brains, whereas caudate is affected relatively less. Areas of damage were 35% for pretreated brains and 38% for the untreated brains.

such as nicardipine on metabolic, histologic, and clinical outcomes in both animal and human studies of cerebral ischemia [10].

We found, however, that at the dose used (10  $\mu\text{g}/\text{kg}$  bolus and 8  $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$  maintenance), the efficacy of nicardipine as a cerebroprotective agent was seriously compromised by elevated blood glucose. Compared with normoglycemic drug-treated animals, hyperglycemic cats injected with nicardipine had significantly reduced levels of high-energy phosphates, elevated lactic acid, and larger ischemic lesions in the occluded MCA territory. It is not clear why nicardipine's protective action would be reduced in hyperglycemic stroke conditions. This calcium channel blocker is highly lipophilic because of the tertiary amine structure in the ester side chain, and thus is readily able to penetrate cell membranes. Also, in the low pH conditions found in ischemia, nicardipine is almost completely protonated and hence is preferentially sequestered in acidotic tissues [17]. A recent study [8] found that, unlike nicardipine, the dihydropyridine calcium channel blocker nimodipine prevented enhanced cerebral acidosis in hyperglycemic MCA-occluded rats. However, neither local cerebral blood flow nor infarct size 4 hr after occlusion was influenced by nimodipine administration, which makes the mechanism of action of the drug difficult to interpret.

Previous work has shown that hyperglycemia exaggerates ischemic brain damage by enhancing tissue lactic acid formation and impairing normal phosphorus metabolism [1, 18–20]. In a recent  $^{31}\text{P}$  MR spectroscopic study in a patient with a large hemispheric stroke, persistent hyperglycemia was associated with prolonged acidosis and failure of high-energy phosphorus metabolism [18], which is in agreement with our findings of low intracellular pH and elevated inorganic phosphate in the MCA territory of hyperglycemic animals after occlusion. Conversely, maintenance of normoglycemia has been associated with an accelerated recovery of normal high-energy phosphate levels, a reduction in acidosis, and an improved functional outcome [1, 21, 22]. It has been suggested that prolonged acidosis in the focus of cerebral infarction may be a prognostic marker of adverse neurologic outcome [18].

Brint et al. [23] noted increased infarct volume in hyperglycemic rats after MCA and common carotid artery occlusion. Elevated plasma glucose was also associated with larger infarct size and mortality in a cat model of MCA occlusion [24–26]. The deleterious effects of elevated blood glucose may be dependent on the degree of regional and local blood flow disturbances following stroke. Prado et al. [26] found that hyperglycemia increased infarct volume in collaterally perfused regions, such as neocortex, but not in end-arterial vascular territories, such as the basal ganglia. It has been suggested [26–28] that in collaterally perfused tissues the degree of tissue acidosis in partially ischemic marginal zones may be influenced by the continuing transport of glucose from blood to brain. Regions of nonanastomosing vascular supply, such as the caudate and putamen, are not subjected to high blood glucose levels after ischemia, since no collateral circulation is available [29]. These data suggest that lacunar infarcts, which result from occlusion of end-arterial vascular beds [30], would not be adversely affected by hyperglycemia.

In this regard, it is of interest that a recent prospective study of 252 acute stroke patients reports a significantly higher correlation between admission glucose level and mortality and morbidity when data from cortical and lacunar infarcts were pooled than when they were assessed separately [31].

Not all experimental and clinical studies are in agreement that hyperglycemia has a deleterious impact on infarct size and functional outcome after cerebral ischemia. Adams et al. [32] prospectively compared admission serum glucose concentration with neurologic outcome in 65 patients treated with naloxane after acute or progressing cerebral infarction. Functional outcome and the volume of infarcts on CT were significantly correlated with the severity of neurologic deficits at admission, but not with serum glucose concentration. A few other studies [33, 34] also have failed to find a significant correlation between serum glucose concentration at admission and the subsequent functional outcome.

Finally, in at least two recent animal model studies [35, 36], hyperglycemia actually reduced the extent of experimental brain infarction. Zasslow et al. [36] induced hyperglycemia in cats prior to clip ligation of the left MCA. Six hours later the area of severe ischemic neuronal damage in the cortex of the hyperglycemic group was smaller than in normoglycemic controls. Comparisons with our study are difficult to make, however, because Zasslow et al. used a different anesthetic (halothane), induced a severe hyperglycemia (561 vs 250–300  $\text{mg}/\text{dl}$  in our present study), and analyzed only cortical tissues.

Considered together, these data suggest that carefully controlled prospective clinical trials are needed to establish unequivocally the influence of serum glucose in cerebral ischemic injury. On balance, the majority of current studies indicate that glucose-containing solutions should not be provided to patients with acute ischemic stroke.

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