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Glucose Administration before Cardiac Arrest Worsens Neurologic Outcome in Cats

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The effects of glucose on neurologic and neuropathologic outcome following global cerebral ischemia were examined in 20 cats subjected to 14 min of cardiac arrest, followed by closed chest resuscitation and intensive care monitoring. Beginning 30 min prior to cardiac arrest, 15 ml/kg of 5% dextrose in 0.45% saline or the same volume of 0.9% saline was administered in a blinded fashion over 15 min. Ventricular fibrillation was electrically induced and cardiac resuscitation was performed according to a standardized protocol, which included closed chest cardiac compressions, epinephrine, lidocaine, sodium bicarbonate administration, and electrical defibrillation. Animals not resuscitated within 4 min were excluded from further study. Resuscitated animals were managed in an intensive care setting for 24 h postresuscitation. Neurologic deficits were scored at 2, 4, and 7 days postresuscitation. Subsequently, the animals' brains underwent histologic examination. Nine cats were excluded from data analysis. Three did not meet protocol criteria and six could not be resuscitated within 4 min. As a result of a technical error, the brain of one glucose-treated cat was not analyzed. Six saline-treated and five glucose-treated animals met all protocol criteria and survived for 7 days postresuscitation. Plasma glucose concentration before cardiac arrest was 118 ± 24 mg/dl (mean ± SD) in the saline group and 269 ± 21 mg/dl in the glucose group ($P < 0.01$). Neurologic outcome rank at 2, 4, and 7 days postresuscitation was significantly worse in glucose-treated cats ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively). The neuropathologic score did not differ between glucose- and saline-treated groups ($P = 0.07$). This study demonstrated that a clinically relevant dose of glucose administered prior to cardiac arrest exacerbates postresuscitation neurologic injury in a feline cardiac arrest model of global cerebral ischemia. (Key words: Brain: anoxia; EEG; histopathology; ischemia. Complications: cardiac arrest. Metabolism: glucose; hyperglycemia.)

RECENT ANIMAL STUDIES, using various models of cerebral ischemia, have shown that hyperglycemia existing prior to cerebral ischemia worsens subsequent neurologic and/or histologic outcome.[1–5] However, to our knowledge, no studies have examined the effects of modest hyperglycemia on long-term (7 day) neurologic outcome in the biochemically and pharmacologically complex setting of cardiac arrest and resuscitation. Myers and Yamaguchi[1] unexpectedly found in two monkeys that administration of glucose prior to cardiac arrest and resuscitation markedly augmented the severity of brain injury at 10 or 36 h postresuscitation (PR). Prearrest plasma glucose values were not reported. D'Alecy *et al.*[2] showed that glucose administration both before and after cardiac arrest and resuscitation in dogs significantly worsened neurologic deficits when examined at 24 h postischemia. Prearrest blood glucose was 335 mg/dl (SD was not reported). In these two studies, animals were not observed beyond 36 and 24 h, respectively. In a study reported by Lanier *et al.*,[3] monkeys received a glucose infusion prior to complete cerebral ischemia using a neck tourniquet model. All survived for 96 h postischemia showing greater postischemic neurologic injury than saline-treated animals. In humans retrospective studies suggest a correlation between poor neurologic outcome following resuscitation from cardiac arrest and either elevated blood glucose[6,7] or prolonged resuscitation time.[8] Confounding the issue is an association between elevations in blood glucose and prolonged resuscitation times.[8] A conclusive association between increased plasma glucose and impaired neurologic function following resuscitation from cardiac arrest has never been demonstrated in humans.

The purpose of the current study was twofold: 1) to prospectively determine if modest elevations of plasma glucose prior to ischemia would significantly worsen long-term (7 day) neurologic outcome in cats subjected cardiac arrest and resuscitation (We believe that the model used in the current study more closely simulates a clinical cardiac arrest than models used in previously performed studies.); and 2) to determine if the cat cardiac arrest model as currently employed was capable of distinguishing differences in neurologic outcome when such differences would be expected to exist.

Materials and Methods

This protocol was approved by the Animal Subjects Committee of the University of California, San Diego. Twenty colony bred cats, ages 3–5 months, weighing 1.7–2.5 kg, were studied. They received only water *ad libitum* for the 16–20 h prior to study. The animals were anesthetized with 4% halothane in oxygen delivered into a Plexiglas box. Peripheral venous cannulae were placed in both forelegs, and 0.3 mg/kg pancuronium was injected

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intravenously (iv) to facilitate endotracheal intubation with a 4 mm internal diameter cuffed endotracheal tube. The inspired concentration of halothane was then decreased to 1.0–1.5% in 70% nitrous oxide and oxygen. Animals were placed in the supine position and mechanically ventilated with a tidal volume of 15 ml/kg 5 cm H_2O positive end-expiratory pressure (PEEP), and a respiratory rate adjusted to maintain normocarbia (Pa_{CO_2} = 30–35 mmHg). Esophageal temperature, the electrocardiogram (ECG) and end-tidal CO_2 (Accucap O_2/CO_2 Monitor, Datascope, Paramus, New Jersey) were monitored continuously. The electroencephalogram (EEG) was recorded from frontooccipital (Fz-Oz) and biparietal (C3-C4) leads (Model 78, Grass, Quincy, Massachusetts). Animals received an infusion of normal saline at 4 $ml \cdot kg^{-1} \cdot h^{-1}$ and pancuronium at 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$. Using aseptic technique and after skin infiltration with 1 ml of 0.25% bupivacaine, cannulae were passed into the distal abdominal aorta and the right atrium (RA) *via* the left femoral artery and vein, respectively. A wire (0.4 mm in diameter) was inserted such that its tip protruded 2–5 mm beyond the distal end of the RA cannula with position confirmed by ECG. The mean arterial pressure (MAP), RA pressure (RAP) (both referenced to the level of the RA), ECG, and EEG were continuously recorded on a polygraph recorder (Model 2758, Hewlett-Packard, Waltham, Massachusetts). After closure of the groin wound, the inspired concentration of halothane was decreased to 0.5%. After 15 min in a blinded and random fashion the animals were assigned to one of two treatment groups and received either 0.9% saline or 5% dextrose in 0.45% saline at a rate of 1 $ml \cdot kg^{-1} \cdot min^{-1}$ for 15 min. Fourteen minutes after completing the test fluid infusion, halothane was discontinued, and 1 min later cardiac arrest was initiated.

Cardiac arrest and resuscitation were performed as previously described by Todd *et al.*[9] with minor modification. MAP, RAP, heart rate, esophageal temperature, end-tidal CO_2 concentration, arterial blood gases, *p*H (IL-813, Instrumentation Laboratory, Lexington, Massachusetts), and plasma glucose (Glucose analyzer 23A, YSI, Yellow Springs, Ohio) were measured at the start and end of the test fluid infusion and 1 min before discontinuing halothane (2 min before the start of cardiac arrest). Plasma osmolality, hematocrit, and plasma electrolytes (Na/K Ion analyzer, Nova Biomedical, Waltham, Massachusetts) were measured prearrest. Ventricular fibrillation (VF) was induced by passing a 20-V, 60-Hz alternating current between the RA wire and a subcutaneous precordial needle. Ventilation was simultaneously discontinued and the endotracheal tube was occluded. The fibrillating voltage was tapered to zero during the first minute of the arrest period. However, if spontaneous defibrillation occurred within the first minute, the voltage was increased and the tapering repeated. Animals with any spontaneous heart beat more than 1 min into the arrest period were discarded. At 4 min into the arrest period, the RA wire and subcutaneous needle were removed. At 13.5 min after the induction of VF mechanical ventilation was resumed with 100% oxygen at a respiratory rate 50% above the prearrest level. At 14 min after the induction of VF (time 0 PR) cardiopulmonary resuscitation (CPR) was initiated. The thorax was compressed between the lateral walls of the rib cage at a rate of 100–120 compressions per min. Efforts were made to maintain systolic pressure greater than 100 mmHg. Epinephrine 15 μg/kg, lidocaine 0.6 mg/kg, and sodium bicarbonate 1.0 mEq/kg were injected *via* the RA cannula simultaneously with the initiation of CPR and every 60 s thereafter. After 2 min of CPR, a 25-joule DC shock was applied between two chest paddles (DC Defibrillator 640, Physiocontrol, Redmond, Washington) placed on the shaved lateral chest walls. If necessary, a DC shock was repeated at 3 and again at 3.75 min until defibrillation occurred. All animals received 30–60 μg/kg atropine after restoration of a spontaneous heart beat.

Resuscitation was considered successful if systolic blood pressure was maintained above 100 mmHg without CPR by 4 min PR. Controlled ventilation was continued with muscle paralysis provided by pancuronium. To minimize the stress of immobilization, midazolam 0.5 mg/kg iv as a bolus followed by 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ by infusion was started at 1 h PR. The inspired gas mixture was changed to 40% oxygen in nitrogen at 3 h PR. All animals received 5 cm H_2O PEEP, which was increased up to 10 cmH_2O as needed to maintain Pa_{O_2} greater than 100 mmHg. Monitoring of MAP, RAP, end-tidal CO_2, ECG, and EEG and intermittent analysis of arterial blood gases and plasma glucose were continued during the intensive care period.

The MAP was carefully maintained between 90 and 110 mmHg. Hypotension (MAP < 90 mmHg) was treated by incremental administration of lactated Ringer's solution (total not to exceed 40 ml) and infusion of norepinephrine. Hypertension (MAP > 110 mmHg) was treated by infusion of trimethaphan. Metabolic and/or respiratory acidosis were corrected by administration of bicarbonate (1 mEq increments) and/or by an increase in respiratory rate, respectively. The maintenance fluid was changed from normal saline to 5% dextrose in 0.45% saline solution at 6 h PR. Animals were turned and their tracheas suctioned every 4 h. Cefazolin 50 mg was administered intramuscularly at the end of surgery and every 12 h (until 48 h PR).

At 20 h PR infusion of pancuronium and midazolam was discontinued. After spontaneous muscle activity was observed 60 μg/kg neostigmine and 40 μg/kg atropine were administered iv to reverse any residual muscle relaxant effect and to avoid bradycardia, respectively. The

trachea was extubated after Pa_{CO_2} was maintained below 40 mmHg during spontaneous ventilation. The arterial and RA cannulae were removed (1–1.5% halothane in oxygen by mask as needed). Extubated animals were placed in a Plexiglas cage with the ambient temperature maintained at 25° C. Oxygen (5 l/min) was supplied until 48 h PR. An infusion of 5% dextrose in 0.45% saline was continued until 48 h. Thereafter, strained baby food and water were given po or *via* gastric tube as indicated.

Arterial blood gases and *p*H were measured at 5, 10, 30, and 45 min and 1 h PR, then every hour until 6 h PR, and thereafter every 2 h until the time of removal of cannulae (20–24 h PR). Plasma glucose was determined at 5, 10, and 30 min and 1 h PR, and then every 4 h. Plasma electrolytes were determined at 5 min PR, and 1, 4, 12, and 20–24 h PR. Total volume of blood sampled from each animal averaged 25 ml over 24 h.

Neurologic examination was performed at 2, 4 and 7 days PR by two observers blinded to the treatment groups. The animals were graded using the Neurologic Deficit Score (NDS) described by Tateishi *et al.*[10] (table 1). Cats were graded according to their level of consciousness, respiratory pattern, cranial nerve responses, muscle tone, motor responses to noxious stimuli, behavioral reactions, stance, and gait. A score of 0 indicated a normal animal and 100 indicated brain death. A score was awarded by each of the two blinded observers and the NDS for each day was taken as the average of the two scores.

After the day 7 observation, animals were anesthetized with pentobarbital 30 mg/kg ip and perfused *via* the left ventricle with normal saline followed by 10% buffered formalin phosphate solution at a pressure of 100 mmHg. The brain was removed and placed in 10% buffered formalin phosphate solution for at least 2 weeks prior to histologic examination. Neuropathologic examination was performed as described by Tateishi *et al.*[10] Briefly, coronal slices of the left frontal cortex, occipital cortex, hippocampus, and sections of the cerebellar hemisphere were dehydrated in a graded series of alcohols, cleared in xylene, and embedded in paraffin. Sections were cut at a thickness of 6 μm and stained with hematoxylin and eosin. Histologic evaluation was performed by two observers (M.R.G., M.H.Z.) who were blinded to the treatment groups and neurologic scores. Ischemic neurons were identified by the presence of shrunken, eosinophilic cytoplasm and homogeneous, pyknotic, or fragmented nuclei. Histologic sections were graded according to the frequency of ischemic neurons in defined regions of each section: 0 = normal, 1 = rare (<10%), 2 = frequent (10–50%), and 3 = majority (>50%). In the hippocampal sections: 0 = normal, 1 = rare ischemic pyramidal or granule cells, 2 = focal ischemic damage, and 3 = severe, diffuse ischemic damage. The total neuropathologic score for each animal was obtained by summing the scores from the four regions. Accordingly, best and worst possible scores for an animal were 0 and 12, respectively.

TABLE 1. Neurologic Deficit Score Scale

Level of consciousness (maximum 15)	
Normal	0
Clouded or delerious	5
Suporous	10
Comatose	15
Respiration (maximum 5)	
Normal	0
Abnormal	5
Cranial nerve function (maximum 14)	
Vision (present/absent)	0–2
Light reflex (present/absent)	0–2
Oculocephalic reflex (present/absent)	0–2
Corneal reflex (present/absent)	0–2
Facial sensation: hemostat to nasal septum (present/absent)	0–2
Auditory response (loud clap) (present/absent)	0–2
Gag reflex: tongue blade to posterior pharynx (present/absent)	0–2
Muscle tone and motor responses (maximum 16)	
Muscle tone/position	
Trunk (normal 0/spastic 2/flaccid 4)	0–4
Limbs (normal 0/spastic 2/flaccid 4)	0–4
Flexor reflex to pain: pressure on base of toenail	
Front (present 0/abnormal 2/absent 4)	0–4
Hind (present 0/abnormal 2/absent 4)	0–4
Behavioral reactions (maximum 20)	
Wheelbarrowing: gait on forelimbs when hind limbs are held off ground (present 0/abnormal 2/absent 4)	0–4
Extensor postural thrust: lower animal with hind limbs just touching floor, allow walking (present 0/abnormal 2/absent 4)	0–4
Placing: paws contact table edge, simultaneously and individually; observe for placement onto table	
Front (present 0/abnormal 2/absent 4)	0–4
Rear (present 0/abnormal 2/absent 4)	0–4
Feeding (yes 0/swallows 1/absent 2)	0–2
Cleaning (present 0/absent 2)	0–2
Gait (maximum 30)	
Normal	0
Minimal ataxia (able to walk without falling)	5
Moderate ataxia (walks but falls frequently)	10
Able to stand independently (cannot walk > 3 steps)	15
Unable to stand independently (stands with assistance)	20
Unable to stand even with assistance; purposeful movement is present	25
No purposeful movement (no response to painful stimulus)	30
Maximum possible total	100

EXCLUSIONS

Animals were excluded from data analysis if any of the following conditions occurred: prearrest plasma glucose > 180 mg/dl in saline-treated animals; any spontaneous heart beat more than 1 min into the arrest period; CPR period > 4 min; systolic blood pressure < 100 mmHg at 4 min PR without CPR; Pa_{O_2} < 70 mmHg and/or Pa_{CO_2} > 50 mmHg for more than 30 min; MAP < 70

mmHg or >130 mmHg for more than 60 min, MAP < 50 mmHg at any point; or evidence for a noncerebral cause of death (*e.g.*, pneumothorax, pneumonia, cardiac failure).

STATISTICS

Comparisons of physiologic variables between groups were carried out with a two-factor repeated-measures ANOVA. When indicated, further analysis was performed with unpaired *t* tests. The Mann-Whitney rank-sum test was used to identify intergroup differences in NDS and neuropathologic score. Intragroup differences in NDS over time were analyzed with a nonparametric paired *t* test. Correlations between neurologic and histologic scores were evaluated by Spearman's rank-sum coefficient. The Fisher exact test was used to test for differences in the incidence of burst–suppression EEG activity. All data are presented as mean ± SD. Differences associated with $P < 0.05$ level of probability were considered statistically significant.

Results

Nine of the 20 cats studied were excluded from data analysis. One saline-treated cat was omitted because of an elevated prearrest plasma glucose level (182 mg/dl). Six cats could not be resuscitated within 4 min. In two saline-treated and three glucose-treated animals the reasons were unclear, and in one saline-treated cat, autopsy revealed a small hole in the RA wall. One saline-treated cat died of a pneumothorax at 4 h PR and one glucose-treated cat died following pulmonary aspiration at 2 days PR. The remaining 11 animals (six saline-treated and five glucose-treated) were entered into the data analysis. As a result of a technical error, the brain of one glucose-treated cat was not analyzed.

The saline-treated and glucose-treated groups were well matched for body weight (2.0 ± 0.2 kg *vs.* 1.9 ± 0.1 kg, respectively) and sex (two males *vs.* three males, respectively). There was no difference between groups in the duration of halothane anesthesia (121 ± 21 min saline *vs.* 117 ± 15 min glucose). No animal displayed a pulsatile blood pressure immediately following the fibrillating current, and all animals had an isoelectric EEG 2 min after the onset of VF. All saline-treated cats and two glucose-treated cats were resuscitated after the first DC shock, and a second DC shock was necessary in the other three glucose-treated cats (NS). The resuscitation time (129 ± 6 s saline *vs.* 154 ± 39 s glucose) and total doses of drugs used during CPR were not significantly different between groups.

Table 2 presents physiologic variables for the glucose-treated and saline-treated groups. There were no differences in prearrest physiologic variables between groups. MAP was maintained between 90 and 110 mmHg in both groups PR. There were no significant differences between groups in the total doses of norepinephrine, trimethaphan, or lactated Ringer's solution administered. There were no significant differences in arterial blood gases between groups at any time. Plasma glucose was significantly greater in the glucose-treated group both prearrest (118 ± 24 mg/dl saline *vs.* 269 ± 21 mg/dl glucose) and at 30 min PR (236 ± 93 mg/dl saline *vs.* 364 ± 81 mg/dl glucose). There were no significant differences between groups in hematocrit or plasma electrolytes at any time or in prearrest osmolality.

There was no significant difference between groups in the time to first appearance of any EEG activity (30 ± 10 min saline *vs.* 23 ± 7 min glucose), nor was there any correlation between return of EEG activity and NDS, irrespective of study group. Two patterns of EEG recovery

TABLE 2. Selected Physiologic Variables Preresuscitation and Postresuscitation

Variable	Group	Prearrest	5 min PR	30 min PR	1 h PR	4 h PR	8 h PR	12 h PR	24 h PR‡
MAP (mmHg)	S	119 ± 13	87 ± 26	110 ± 17	96 ± 9	98 ± 7	104 ± 6	105 ± 7	102 ± 17
	G	121 ± 19	82 ± 21	101 ± 21	95 ± 12	105 ± 5	96 ± 5	100 ± 7	94 ± 15
HR (beats/min)	S	188 ± 27	217 ± 48	241 ± 25	245 ± 22	201 ± 7	218 ± 28	211 ± 27	187 ± 19
	G	194 ± 21	282 ± 36	232 ± 55	255 ± 27	218 ± 31	209 ± 23	224 ± 28	195 ± 46
Temperature (° C)	S	37.4 ± 0.2	36.9 ± 0.7	37.0 ± 0.4	37.7 ± 0.4	37.6 ± 0.2	37.9 ± 0.4	37.5 ± 0.3	37.6 ± 0.2
	G	37.6 ± 0.2	36.9 ± 0.1	37.2 ± 0.5	37.6 ± 0.2	37.3 ± 0.2	37.3 ± 0.1	37.5 ± 0.2	37.4 ± 0.2
*p*H	S	7.42 ± 0.05	7.27 ± 0.17	7.43 ± 0.04	7.45 ± 0.05	7.44 ± 0.02	7.41 ± 0.03	7.42 ± 0.04	7.45 ± 0.02
	G	7.44 ± 0.07	7.23 ± 0.13	7.46 ± 0.11	7.46 ± 0.05	7.45 ± 0.05	7.44 ± 0.05	7.44 ± 0.02	7.42 ± 0.06
Pa_{CO_2} (mmHg)	S	32 ± 3	47 ± 6	30 ± 3	28 ± 3	34 ± 3	35 ± 5	32 ± 1	30 ± 3
	G	30 ± 3	53 ± 7	32 ± 3	33 ± 2	31 ± 2	33 ± 5	32 ± 3	31 ± 6
Pa_{O_2} (mmHg)	S	158 ± 25	398 ± 30	472 ± 32	408 ± 159	210 ± 20	199 ± 23	205 ± 16	448 ± 41
	G	180 ± 12	352 ± 53	446 ± 7	418 ± 92	215 ± 72	195 ± 22	190 ± 25	448 ± 37
Plasma glucose (mg/dl)	S	118 ± 24	376 ± 144	236 ± 93	215 ± 69	169 ± 90	211 ± 54	231 ± 44	223 ± 51
	G	269 ± 21†	537 ± 133	364 ± 81*	269 ± 45	220 ± 78	189 ± 41	226 ± 67	215 ± 41
Hematocrit (%)	S	29 ± 2	28 ± 2	—	31 ± 4	31 ± 4	30 ± 5	27 ± 5	23 ± 2
	G	28 ± 2	28 ± 7	—	30 ± 5	31 ± 7	29 ± 3	27 ± 4	24 ± 3

Data are expressed as mean ± SD. S = saline (n = 6); G = glucose (n = 5).

Significantly different from saline group; *$P < 0.05$; †$P < 0.01$.
‡ 24 h PR or time of cannulae removal.

were distinguished: 1) recovery with slow δ wave activity, and 2) recovery with bursts of 10–20 Hz activity mixed with periods of suppression. Burst–suppression type activity was observed in all glucose-treated cats and one saline-treated cat ($P = 0.007$). In three glucose-treated cats and the one saline-treated cat that showed EEG recovery with bursts, EEG activity changed into continuous slow activity prior to 1 h PR. The other three glucose-treated cats showed burst activity continuously until 1 h PR (time of midazolam administration). There was a positive correlation ($P < 0.05$) between the occurrence of burst–suppression type activity and worse 7 day NDS. No clinical evidence of seizure activity was noted during the study.

There were significant differences in 2, 4, and 7 day NDS rank between groups ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (fig. 1). In the saline-treated group, all animals had a normal level of consciousness at day 2, and neurologic recovery at day 7 was complete (NDS = 0) in one cat and almost complete (NDS = 2) in three cats. In the glucose-treated group, three cats had a clouded level of consciousness and all had behavioral and gait abnormalities at day 7. In the glucose-treated cats NDS did not change between days 2, 4, and 7, whereas in the saline-treated cats the NDS was improved on days 4 and 7 compared with day 2 ($P < 0.01$). Neuropathologic scores did not differ between glucose- and saline-treated groups ($P = 0.07$) (fig. 2). However, in the cerebellum, there was significantly greater damage noted in the glucose-treated cats ($P < 0.05$). There were no histologic differences found in the frontal cortex, occipital cortex, or hippocampus. There was no correlation between neuropathologic score and day 7 NDS rank ($P = 0.08$).

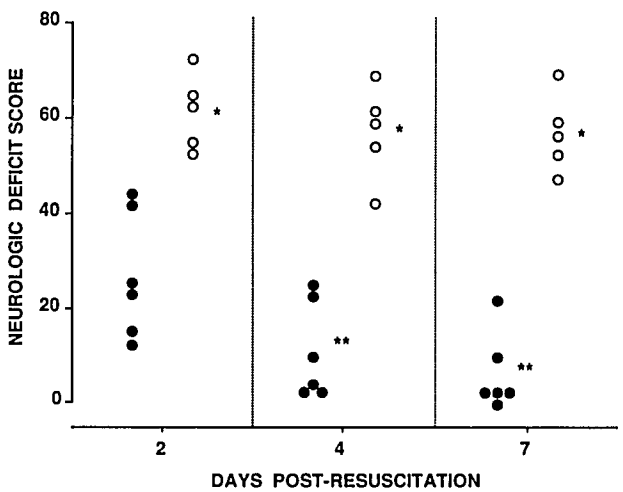

FIG. 1. NDS at 2, 4, and 7 days postresuscitation (0 = normal; 100 = brain death) in glucose-treated (open circles) and saline-treated (filled circles) cats. There were significant differences in NDS between groups at 2, 4, and 7 days (*$P < 0.01$). In the saline-treated animals NDS at 4 and 7 days was significantly less than at 2 days (**$P < 0.05$).

FIG. 2. Neuropathologic score for glucose- and saline-treated cats (0 = no ischemic change; 12 = most severe ischemic change). There was no significant difference in the neuropathologic score between groups ($P = 0.077$). As a result of a technical error, the brain of one glucose-treated cat was not analyzed.

Discussion

The mechanism by which increased brain glucose, as measured by increased plasma glucose prior to complete cerebral ischemia, results in exacerbation of cerebral injury is proposed to be *via* increased anaerobic glucose metabolism and accompanying lactic acidosis.[11–14] Many studies have examined the relationship between plasma glucose and neuronal injury following cerebral ischemia. In monkeys subjected to 14 min of potassium chloride-induced cardiac arrest, Myers and Yamaguchi[1] reported that the two monkeys that received 5% glucose in physiologic saline (approximately 35 and 75 ml/kg, respectively) prior to ischemia had greater postischemic neurologic injury than three saline-treated monkeys. The two glucose-treated monkeys remained comatose and exhibited widespread muscular fasciculations progressing to generalized myoclonic seizures. D'Alecy *et al.*[2] found that in dogs subjected to 8 min of cardiac fibrillation and resuscitated with open chest cardiac massage, those given 5% glucose in lactated Ringer's solution both precardiac arrest and postcardiac arrest (total approximately 42 ml/kg) had greater postischemic neurologic deficits at 24 h than those without glucose treatment. Plasma glucose levels pre-ischemia were 129 mg/dl (n = 2) in lactated Ringer's solution-treated animals and 335 mg/dl (n = 3) in glucose-treated animals. Four of five resuscitated dogs treated with glucose displayed convulsive activity and died by 9 h after cardiac arrest, whereas all six lactated Ringer's solution-treated dogs survived and at 24 h PR were able to walk and eat. Lanier *et al.*[3] administered approximately 15 ml/kg iv of 5% dextrose in 0.45% saline to monkeys

30 min before complete cerebral ischemia using a neck tourniquet model. Neurologic outcome at 96 h postischemia and histopathology were significantly worse in glucose-treated monkeys than in lactated Ringer's solution-treated monkeys. Interestingly, pre-ischemic mean blood glucose concentration in the glucose-treated animals was not statistically different from that in the lactated Ringer's solution-treated animals (181 ± 19 and 140 ± 6 mg/dl, respectively, $P = 0.07$, mean ± SE). Siemkowicz and Hansen[4] observed that six hyperglycemic rats (pre-ischemic blood glucose 432 ± 22 mg/dl, mean ± SD) showed seizure activity and died within 12 h following 10 min complete cerebral ischemia (neck tourniquet), whereas ten normoglycemic rats (pre-ischemic blood glucose 140 ± 25 mg/dl) survived for 21 days and recovered with minor gait abnormalities. Pulsinelli *et al.*[5] found that seven of ten rats made hyperglycemic (3 gm/kg ip, plasma glucose approximately 300 ± 30 mg/dl, mean ± SD) prior to severe forebrain ischemia (four vessel occlusion) convulsed during the 24-h recovery period; five of these animals died. The other five surviving rats had difficulty walking at 24 h. None of the normoglycemic animals convulsed and all walked normally at 24 h. The hyperglycemic animals developed ischemic damage throughout the forebrain and severe brain edema, whereas normoglycemic rats suffered no more than scattered damage of selectively vulnerable neurons and had no increase in brain water content.

These previously reported studies have examined situations that are poor analogies of common clinical situations. In some situations the increases in plasma glucose have been extreme,[2,4,5] in others, the cerebral ischemia has been isolated to the cerebral circulation rather than the entire systemic circulation.[3] In two studies[1,2] the circumstance of total body ischemia (*i.e.*, cardiac arrest) was examined; however, animals were not followed beyond 24–36 h. The current study sought to avoid the shortcomings of these previous studies.

In a clinical retrospective study of patients receiving CPR following out-of-hospital cardiac arrest, blood glucose increased with CPR duration but did not correlate with eventual awakening.[8] This lead the authors to conclude that, "the longer the resuscitation, the higher the rise of blood glucose, the less likely the patient will awake."[8] Consequently, the role of increased plasma glucose in contributing to adverse neurologic outcomes is not clear. The current study has clarified the specific effects of glucose on long-term neurologic outcome in a total body ischemia model that simulates the clinical situation of cardiac arrest and resuscitation but in which the details and duration of resuscitation were well standardized.

Previous studies performed in our laboratory using the cat cardiac arrest model have examined the effects of thiopental,[9] nimodipine,[10] MK-801,[15] and emopamil (unpublished data) on neurologic outcome and cerebral histopathology. In none of these studies were there found to be any differences in end points between treated and untreated animals. There are two possible conclusions that one can draw from this information. One is that none of the drugs examined alters neurologic or histologic outcome. The other is that the agents tested are effective and do improve neurologic or histologic outcome, but the model may not have the sensitivity required to identify such subtle improvements. The current study has demonstrated that the model is capable of demonstrating a worsening of neurologic outcome when such an effect would be expected.

As noted, it has been shown that poor neurologic outcome in patients suffering cardiac arrest is associated with both hyperglycemia and prolonged CPR.[16,17] However, the cause-and-effect relationships are not clear and the question then arises whether cardiac resuscitation is more difficult in the presence of an elevated blood glucose.[18] In the present study there were no differences in resuscitation times or drug doses between groups. Nor was there any difference in the number of unsuccessful resuscitations between groups. Similarly, D'Alecy *et al.*[2] found no significant difference in resuscitation times between normoglycemic and hyperglycemic dogs. These findings suggest that although hyperglycemia or prolonged resuscitation times are associated with poor neurologic outcome, hyperglycemia *per se* does not appear to be associated with prolonged resuscitation times.

In the present study significant differences in NDS were apparent between groups as early as day 2 PR. In the saline-treated animals NDS continued to improve (decrease) on days 4 and 7. These findings result from multiple factors, including the duration of ischemia and the amount of glucose administered. It is possible that with minor changes in protocol the subsequent changes in neurologic outcome would not have been apparent until 4 or even 7 days postischemia. This highlights the importance of evaluating neurologic end points over more than 1–2 days in studies of this nature.

In conclusion, the present study demonstrated that administration of a clinically commonplace volume of 5% dextrose solution (15 ml/kg) prior to a 14-min cardiac arrest significantly worsens subsequent neurologic outcome. These findings confirm that, in the physiologically complex circumstance of cardiac arrest and a standardized resuscitation, the modest increases in plasma glucose that occur from routine use of dextrose-containing solutions result in obvious worsening of the subsequent neurologic injury.

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