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Effects of Temperature on Cerebral Tissue Oxygen Tension, Carbon Dioxide Tension, and pH during Transient Global Ischemia in Rabbits

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Background: A decrease in brain temperature (T_{brain}) causes a decrease in the cerebral metabolic rate for oxygen (CMRO_2) and provides potent neuroprotection against ischemic damage. In the present study, the effects of mild to moderate hypothermia on cerebral tissue oxygen tension (P_{O_2} brain), carbon dioxide tension (P_{CO_2} brain), and pH ($p\text{H}_{\text{brain}}$) were monitored during short episodes of global cerebral ischemia.

Methods: After approval by the Animal Care and Use Committee, 10 New Zealand white rabbits were anesthetized (1% halothane in air) and mechanical ventilation was adjusted to maintain the arterial carbon dioxide tension at 35 mmHg (α -stat). A sensor to measure P_{O_2} brain, P_{CO_2} brain, $p\text{H}_{\text{brain}}$, and T_{brain} was inserted into the brain through a burr hole in the skull. T_{brain} was adjusted to 38°C, 34.4°C, and 29.4°C in a random sequence in each animal. P_{O_2} brain, P_{CO_2} brain, and $p\text{H}_{\text{brain}}$ (all variables are reported at the actual T_{brain}) were recorded every 10 s during a 5-min baseline, 3 min of cerebral ischemia induced by inflation of a neck tourniquet, and 10 min of reperfusion at each level of T_{brain} . Analysis of variance and Dunnett's test were used for statistical analysis. Data are presented as means \pm SD.

Results: During ischemia, P_{O_2} brain decreased from 56 ± 3 to 33 ± 2 mmHg at 38°C, from 58 ± 3 to 32 ± 3 mmHg at 34.4°C, and from 51 ± 2 to 32 ± 2 mmHg at 29.4°C ($p = \text{NS}$). P_{CO_2} brain increased by 6.7 ± 2 mmHg at 38°C, by 5.1 ± 1.4 mmHg at 34.4°C, and by 2.3 ± 0.8 mmHg at 29.4°C. $p\text{H}_{\text{brain}}$ inversely followed the trend of P_{CO_2} brain.

Conclusions: The attenuated increase in P_{CO_2} brain during hypothermic ischemia results from the reduced CMRO_2 . The

similar decrease in P_{O_2} brain at all temperature levels indicates that despite the reduction in CMRO_2 , P_{O_2} brain is no better preserved during brief episodes of hypothermic ischemia than during normothermic ischemia. (Key words: Cerebral tissue; hypothermia; extraction; oxyhemoglobin dissociation; New Zealand white rabbit.)

DESPITE the intensive study of a multitude of putative neuroprotective agents,¹⁻⁴ no drug has equaled the potent neuroprotective properties of hypothermia. As a consequence, systemic hypothermia is commonly used during cerebral aneurysm surgery and during open heart surgery, when there is a risk for embolization.⁵⁻⁷ Recently, hypothermia was shown to be of benefit in patients with intracranial hypertension after head trauma.⁸

Various mechanisms have been proposed to explain how hypothermia prevents or attenuates neurologic injury. The most obvious and oldest theory about these mechanisms is that the cerebral metabolic rate for oxygen (CMRO_2) decreases with hypothermia, resulting in prolonged maintenance of aerobic metabolism. Recent studies, however, have shown that during mild hypothermia the neuroprotective effects far exceed the amount that would be predicted from the decrease in CMRO_2 .⁹ It has also been shown that hypothermia substantially attenuates the release of neurotoxic excitatory amino acids during ischemia.¹⁰ These substances are thought to play an important role in ischemia-induced neuronal death.¹¹

The concept that hypothermia protects by preserving cellular energy stores and aerobic metabolism is based on the observation that CMRO_2 is an inverse exponential function of temperature^{12,13}: $Q_{10} = \text{CMRO}_{2a} / (\text{CMRO}_{2b})^{10(T_a - T_b)}$, where Q_{10} is the temperature coefficient ($Q_{10} = 2.2$ between 37°C and 27°C),^{12,13} T_a and T_b are two different temperature levels, and CMRO_{2a} and CMRO_{2b} are the values of CMRO_2 at T_a and T_b , respectively. If we assume the value of CMRO_2 at 38°C to be 100%, a 25% decrease in CMRO_2 at 34.4°C and a

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Table 1. Physiological Variables at Baseline and Immediately after the 10-min Reperfusion Period

		Temperature		
	Interval	38.0°C	34.4°C	29.4°C
MAP (mmHg)	Baseline	71 ± 13	76 ± 11	69 ± 17
	Reperfusion	65 ± 12	70 ± 17	68 ± 12
PaO ₂ (mmHg)	Baseline	88 ± 12	98 ± 19	105 ± 9
	Reperfusion	92 ± 13	101 ± 16	104 ± 7
PaCO ₂ (mmHg)	Baseline	36.4 ± 2.2	31.0 ± 1.4*	24.8 ± 1.2*
	Reperfusion	34.5 ± 6.1	28.9 ± 2.8*	23.4 ± 2.1*
pH	Baseline	7.34 ± 0.05	7.39 ± 0.04*	7.42 ± 0.04*
	Reperfusion	7.32 ± 0.06	7.43 ± 0.05*	7.44 ± 0.05*

Values are mean ± SD. Blood gas data have been corrected to body temperature.

MAP = mean arterial pressure; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension.

* Significant difference versus 38.0°C ($P < 0.017$ by factorial ANOVA and Dunnett's test); $n = 10$.

50% decrease in CMRO₂ at 29.4°C therefore can be predicted.

The measurement of cerebral tissue oxygen tension (P_{O₂} brain) may provide insights into the influence of a decrease in CMRO₂ on the cellular oxygen supply under baseline conditions and during ischemia. With the development of continuous, in vivo (intravascular) monitoring techniques of arterial oxygen tension (PaO₂), carbon dioxide tension (PaCO₂), pH, and temperature, very small sensors with acceptable accuracy and precision are now available.¹⁴ The small size of these sensors has led to growing interest in their use as monitors of brain tissue perfusion and oxygenation.^{15,16} Indeed, it has

been shown that changes in cerebral tissue oxygenation or perfusion due to hypocapnia, hypoxemia, or ischemia can be detected reliably with these devices.^{15,16}

The aim of the present study was to elucidate the effects of a decrease in CMRO₂ induced by a decrease in cerebral tissue temperature (T_{brain}) on the cerebral tissue oxygen tension (P_{O₂} brain) during short episodes of global cerebral ischemia.

Materials and Methods

Laboratory Animals

After we received approval from the Animal Care and Use Committee, we studied 10 male New Zealand white

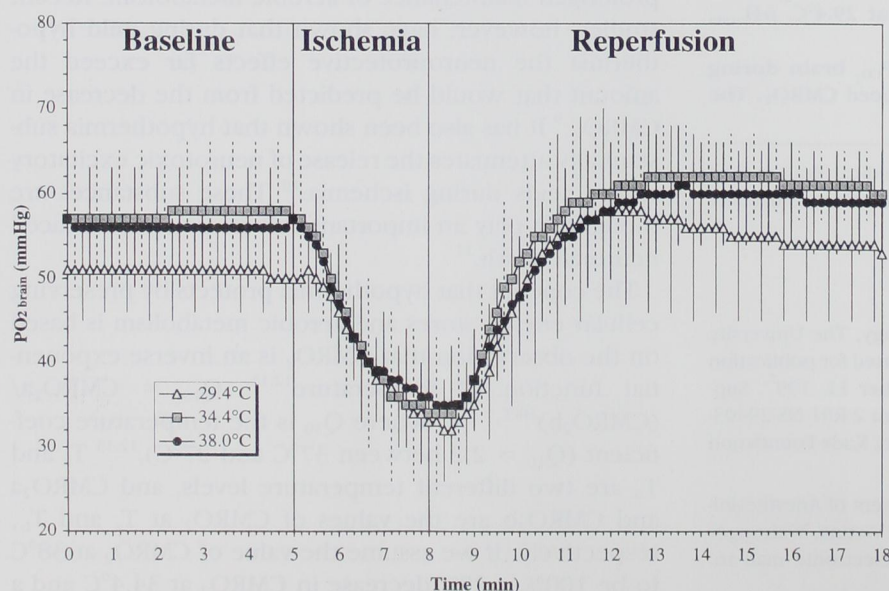
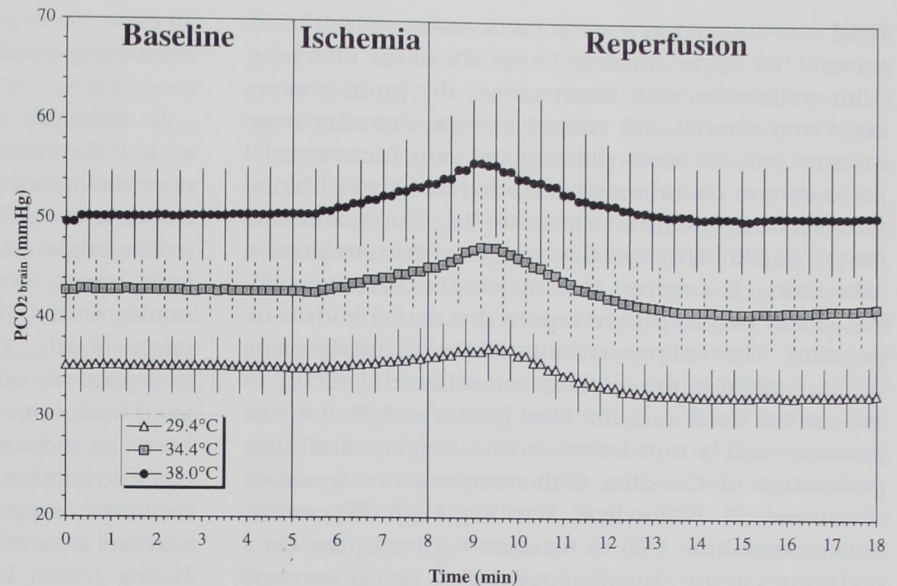


Fig. 1. The time course of cerebral tissue oxygen tension (P_{O₂} brain, means ± SD) during a 5-min baseline, 3 min of global cerebral ischemia, and 10 min of reperfusion at cerebral tissue temperatures (T_{brain}) of 38°C, 34.4°C, and 29.4°C ($n = 10$). For clarity, the SD is shown for every third value in a staggered manner. The values of P_{O₂} brain are given at actual T_{brain}.

Fig. 2. The time course of cerebral tissue carbon dioxide tension (P_{CO_2} brain, means \pm SD) during a 5-min baseline, 3 min of global cerebral ischemia, and 10 min of reperfusion at cerebral tissue temperatures (T_{brain}) of 38°C, 34.4°C, and 29.4°C ($n = 10$). The values of P_{CO_2} brain are given at actual T_{brain} . For clarity, the SD is shown for every third value in a staggered manner.



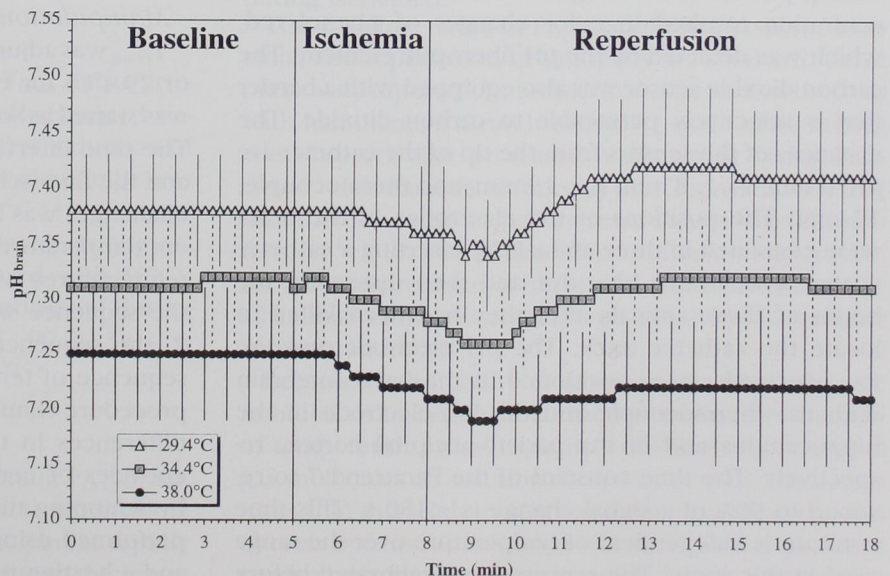
rabbits. The rabbits were 2–3 months old and weighed 3.9 ± 0.5 kg (mean \pm SD). The animals were fasted for 24 h before the start of the experiment and housed one per cage at the institutional Animal Resource Center, where they received routine veterinary care.

Anesthesia, Surgery, and Induction of Global Cerebral Ischemia

The animals were anesthetized in a plastic box by insufflation of 5% halothane in oxygen into the box.

Then endotracheal intubation was performed using a tube with a 3-mm inner diameter and the animals were mechanically ventilated with 1% halothane in air, a tidal volume of 40–60 ml, and a respiratory rate of 12–18/min, adjusted to maintain the arterial carbon dioxide tension (P_{aCO_2}) at 35 mmHg using an α -stat regimen. A catheter was inserted into an ear vein and 0.9% saline was administered at a rate of $5\text{--}10\text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. An additional fluid bolus (40–60 ml) was given if mean arterial pressure decreased to <55 mmHg. The rabbit's

Fig. 3. The time course of cerebral tissue pH (pH_{brain} , means \pm SD) during a 5-min baseline, 3 min of global cerebral ischemia, and 10 min of reperfusion at cerebral tissue temperatures (T_{brain}) of 38°C, 34.4°C, and 29.4°C ($n = 10$). The values of pH_{brain} are given at actual T_{brain} . For clarity, the SD is shown for every third value in a staggered manner.



head was secured in a stereotactic frame, with the interaural line approximately 12 cm above the midchest. After infiltration with bupivacaine, the groin was incised and arterial and central venous cannulas were inserted into the femoral artery and vein. Mean arterial pressure was continuously recorded and arterial blood samples were obtained to measure P_{aO_2} , P_{aCO_2} , and arterial pH (1306 pH /Blood Gas Analyzer; Instrumentation Laboratory, Lexington, MA). Arterial oxygen tension, P_{aCO_2} , and arterial pH are reported at actual body temperature. The scalp was infiltrated with bupivacaine 0.25%, incised in the midline, and reflected laterally to expose the skull. A 2-mm burr hole was drilled 4 mm posterior and 4 mm lateral to the bregma, and after perforation of the dura with microscissors, a sensor (Paratrend 7; Biomedical Sensors, High Wycombe, Buckinghamshire, UK) to measure P_{O_2} brain, the cerebral tissue carbon dioxide tension (P_{CO_2} brain), cerebral tissue pH (pH_{brain}), and T_{brain} was inserted using a 20-gauge arterial cannula and a stereotactic manipulator. The arterial cannula served as an introducer sheath for the sensor and was fixed with its tip at the brain surface. The sensor (0.5-mm diameter) was inserted into the brain to a depth of 4 cm. The burr hole around the arterial cannula was sealed with bone wax. Two optical fibers (to measure P_{CO_2} brain and pH_{brain}), a miniaturized Clark electrode (for P_{O_2} brain), and a thermocouple (for T_{brain}) were located near the tip of the catheter, which was covered with a gas- and ion-permeable microporous polyethylene membrane. The void between the components of the sensor was filled with acrylamide gel containing phenol red. Changes in the hydrogen ion concentration resulted in color changes of phenol red, which was detected by the pH fiberoptic element. The carbon dioxide sensor was also equipped with a barrier that is selectively permeable to carbon dioxide. The distances of the sensors from the tip of the catheter are pH : 6 mm; P_{CO_2} , 8 mm; P_{O_2} , 19 mm; and thermocouple, 17 mm. The positions of the electrodes in the brain were examined in three animals by inserting a catheter coated with Evan's blue dye and then dissecting the brains of those animals after they had been killed to locate the catheter track. The pH electrode and the P_{CO_2} electrode were positioned in the basal forebrain with the thermocouple and the P_{O_2} electrode in the hippocampus and in the parieto-occipital cortex, respectively. The time constant of the Paratrend 7 to respond to 90% of a signal change is <180 s. This time constant is independent of temperature over the range used in this study. The sensors were calibrated before

an experiment according to the manufacturer's instructions using a calibration chamber, calibration gases, and tonometer.

An inflatable neck tourniquet was loosely secured around the rabbit's neck, and the frontoparietal electroencephalogram (EEG) was recorded using needle electrodes and a differential amplifier (model DP-304; Warner Instruments, Hamden, CT). To induce cerebral ischemia, mean arterial pressure was reduced to 30–40 mmHg with a 10–20 mg bolus of trimethaphan given intravenously. The neck tourniquet was then inflated to a pressure of 700 mmHg within 0.5 s using a regulated tank source of compressed air. The time interval between induction of ischemia and the onset of EEG isoelectricity was measured, as was the time from reperfusion to reappearance of the EEG. Three episodes of cerebral ischemia were produced in each animal, each lasting 3 min. To terminate ischemia, the neck tourniquet was deflated, and mean arterial pressure was restored to 80–100 mmHg with a 10–20 μ g bolus of phenylephrine given intravenously. Every 10 s the values of P_{O_2} brain, P_{CO_2} brain, and pH_{brain} were recorded during a 5-min baseline period, during 3 min of ischemia, and during 10 min of reperfusion. Cerebral tissue oxygen tension, P_{CO_2} brain, and pH_{brain} are reported at actual brain temperature.

After the third ischemic episode and collection of all data, the halothane concentration was increased to 5%, and the animals were killed with potassium chloride, 10 mmol given intravenously.

Manipulation of T_{brain}

T_{brain} was adjusted to one of three levels (38°C, 34.4°C, or 29.4°C) for each ischemic episode. Data collection was started as soon as T_{brain} stabilized at the target value. The time intervals between the insertion of the probe and the first ischemia, as well as between the ischemic challenges was 2–3 h. Because we studied three different temperature levels in each animal, six sequences of temperatures were possible (for example, in animal 1, the sequence was 29.4°C, 38°C and 34.4°C; in animal 2, the sequence was 38°C, 34.4°C, and 29.4°C). The sequence of temperature levels was randomized. This procedure eliminated the possible bias originating from differences in the physiologic responses to repeated episodes of cerebral ischemia. Cooling was achieved by wrapping the animal in ice packs. Rewarming was performed using a servocontrolled infrared heat lamp and a heating pad.

Statistical Analysis

To facilitate statistical analysis, the 30 values recorded for each animal during the 5-min baseline period were averaged to yield a single number for P_{O_2} brain, P_{CO_2} brain, and pH_{brain} . Similarly, the 60 values recorded for each animal during the 10-min reperfusion period were averaged. The ischemic value was designated as the lowest (for P_{O_2} brain and pH_{brain}) or the highest (P_{CO_2} brain) value observed during the ischemic period. Analysis of variance was used to compare these averaged values of P_{O_2} brain, P_{CO_2} brain, and pH_{brain} at the three different levels of T_{brain} . Repeated-measures analysis of variance was used to compare baseline values with ischemic and reperfusion values of P_{O_2} brain, P_{CO_2} brain, and pH_{brain} . The change from baseline in these variables during ischemia at 34.4°C and 29.4°C were compared with the changes that occurred at 38°C using factorial analysis of variance and Dunnett's test. Differences in mean arterial pressure, Pa_{O_2} , Pa_{CO_2} , and arterial pH at the three levels of T_{brain} were tested for significance using factorial analysis of variance and Dunnett's test. Data are presented as means \pm SD.

Results

Three episodes of ischemia were induced in each of the 10 animals. One animal died after induction of ischemia at 38°C. Therefore, data from 9 episodes of ischemia at 38°C, 10 episodes at 34.4°C, and 10 episodes at 29.4°C were analyzed.

T_{brain}, Physiologic Data, and Electroencephalogram

At all three target temperature levels, T_{brain} , mean arterial pressure, Pa_{O_2} , Pa_{CO_2} , and arterial pH remained stable during the experiment (table 1). After induction of cerebral ischemia, the time to EEG isoelectricity was almost twice as long at 29.4°C as at 38°C (30 ± 8 s *vs.* 18 ± 6 s; $P < 0.01$). At 34.4°C, EEG isoelectricity occurred after 21 ± 8 s ($P = \text{NS}$ compared with 38°C). Electroencephalographic spikes were observed during reperfusion after 100 ± 67 s at 38°C, 99 ± 54 s at 34.4°C, and 77 ± 20 s at 29.4°C ($P = \text{NS}$).

P_{O₂} brain, P_{CO₂} brain, and pH_{brain}

Figures 1–3 show the course of P_{O_2} brain, P_{CO_2} brain, and pH_{brain} during baseline, ischemia, and reperfusion. After induction of cerebral ischemia, P_{O_2} brain rapidly decreased at all levels of T_{brain} . The maximum decreases

from the mean baseline values were $41 \pm 9\%$ at 38°C, $46 \pm 7\%$ at 34.4°C, and $38 \pm 8\%$ at 29.4°C. During reperfusion, P_{O_2} brain increased within 2 min, reaching maximum values 4–5 min after the start of reperfusion. Thereafter, P_{O_2} brain gradually decreased to baseline values. There were no differences in the trends of P_{O_2} brain during the baseline data recording period, during the ischemic episode, or during the reperfusion period. The decrease in P_{O_2} brain from the mean baseline value to the minimum value observed during ischemia was not significantly different among the three levels of T_{brain} . P_{CO_2} brain remained stable during baseline, increased slightly during ischemia, increased further during the first 1.5 min of reperfusion, and then returned to baseline. As expected, P_{CO_2} brain was significantly lower at 34.4°C and 29.4°C than at 38°C because of the α -stat ventilatory management. The maximum relative increase in P_{CO_2} brain after ischemia compared with the mean baseline values was $13 \pm 10\%$ at 38°C, $12 \pm 7\%$ at 34.4°C, and $7 \pm 6\%$ at 29.4°C. The time course of pH_{brain} showed a stable baseline, a decrease during ischemia that lasted until 1.5 min of reperfusion, followed by an increase and finally stable values between 4.5 and 10 min of reperfusion.

Discussion

The present study shows that a 3-min episode of global cerebral ischemia induces approximately a 40% decrease in P_{O_2} brain. Reduction of T_{brain} to 34.4°C or 29.4°C has no effect on the minimum value of P_{O_2} brain during ischemia.

The absolute values of P_{O_2} brain during baseline, ischemia, and reperfusion in this study are similar to those previously reported. In normothermic cats anesthetized with halothane, a mean baseline P_{O_2} brain of 42 mmHg was observed that decreased to 25 mmHg during ischemia.¹⁵ Halothane is reduced at the Clark electrode and may thereby cause a small increase in measured oxygen tension.^{17,18} However, this effect is of minor importance for the interpretation of the results of this study because all animals continuously received halothane at the same concentration (1%).

Because the solubility of oxygen and carbon dioxide in blood or in extracellular fluid is an inverse function of temperature, the "capacity" of the fluid to contain gas molecules in solution increases at lower temperatures.¹⁹ In this study, α -stat ventilatory management was chosen because it has been shown to better preserve cerebral autoregulation, is associated with a better neu-

ropsychologic outcome after cardiopulmonary bypass procedures, and is more commonly used in clinical practice.^{20,21} With α -stat management, P_{aCO_2} decreases during hypothermia if the P_{aCO_2} is reported at actual body temperature. By necessity, this α -stat management also resulted in lower values for P_{CO_2} brain when measured at 34.4°C and 29.4°C. Arterial oxygen tension and P_{O_2} brain are not affected because of the constant equilibration of pulmonary capillary blood with alveolar oxygen tension.

Despite a predicted decrease in $CMRO_2$ at a lower T_{brain} , no differences in P_{O_2} brain were observed during ischemia. Tissue oxygen tension represents the balance between the rate of oxygen uptake by the cells (*i.e.*, $CMRO_2$) and the affinity of hemoglobin for oxygen. We might have predicted that P_{O_2} brain would be better preserved during ischemia if $CMRO_2$ was decreased. A higher P_{O_2} brain would therefore be expected after a 3-min episode of ischemia during hypothermia. However, P_{O_2} brain depends not only on $CMRO_2$ but also on the amount of oxygen released from the chemical binding to hemoglobin (*i.e.*, oxyhemoglobin dissociation). The degree of oxyhemoglobin dissociation as a function of oxygen tension is described by the oxyhemoglobin dissociation curve.²²⁻²⁴ A decrease in temperature causes a leftward shift of the oxyhemoglobin dissociation curve; that is, at a lower temperature a lower oxygen tension is required to achieve the same amount of capillary hemoglobin desaturation.²³ At least in part, this mechanism could have contributed to the fact that the absolute values in P_{O_2} brain and the decrease during ischemia were similar, independent of temperature. Other factors that influence the movement of oxygen from capillary blood into the interstitial space and cells are the diffusion properties for oxygen of the erythrocyte membranes and of the capillary walls, and the affinity of intramitochondrial cytochromes for oxygen.²⁵ Additional studies are needed to quantify these changes during hypothermia.

Although $CMRO_2$ was not directly measured in the present study, it is likely that it was substantially reduced at 34.4°C and 29.4°C compared with 38°C. This assumption is supported by two independent observations that indicate a decrease in $CMRO_2$. First, the increase in P_{CO_2} brain during ischemia was attenuated at lower temperatures. The increase in P_{CO_2} brain at 29.4°C was almost exactly one half of that observed at 38°C, whereas at 34.4°C it fell between the values obtained at 29.4°C and 38°C. The second factor that may indirectly indicate a decrease in $CMRO_2$ at lower temperatures is

the time until onset of EEG isoelectricity after induction of cerebral ischemia. The trigger mechanisms that cause a cessation of neuronal electrical activity during ischemia are not fully understood. The depletion of intracellular energy stores to a certain critical level that determines the borderline between energy required for neuronal function and for the maintenance of cellular integrity is likely to be associated with the termination of neuronal transmission during ischemia.²⁶ Indeed, it has been shown that the level of $CMRO_2$ before the onset of cerebral ischemia determines the latency of EEG isoelectricity during ischemia.²⁷ In the present study, the mean latencies to EEG isoelectricity at 29.4°C and at 34.4°C were 1.7 and 1.5 times longer than at 38°C, respectively.

In conclusion, the induction of transient global cerebral ischemia caused a marked and reproducible decrease in P_{O_2} brain and pH_{brain} and an increase in P_{CO_2} brain. Despite the predicted decrease in $CMRO_2$ at 34.4°C and 29.4°C, no differences in P_{O_2} brain were observed during baseline, ischemia, or reperfusion compared with these parameters at 38°C. Although the exact reasons for this observation cannot be sufficiently explained by the present data, the leftward shift of the oxyhemoglobin dissociation curve during hypothermia, a change in the diffusion properties of erythrocyte membranes and the capillary walls, and altered oxygen-cytochrome binding may have contributed to this observation. That P_{O_2} brain is not preserved by mild to moderate hypothermia during brief episodes of ischemia provides additional evidence that other mechanisms are important for hypothermic neuroprotection.

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