Brain tissue acid-base changes during ischemia

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It is likely that brain tissue acidosis during ischemia is associated with neuronal injury. The authors measured brain extracellular H^+ , PCO_2 and HCO_3^- concentrations during an ischemic event produced by temporary occlusion of the middle or anterior cerebral arterial distributions, with a 10-minute recovery period. Patients who were to undergo craniotomy for cerebrovascular surgery were recruited for the study. A probe that measures PCO_2 , pH, and temperature was inserted into tissue at risk for ischemia during temporary arterial occlusion. As a control for this treatment, $PaCO_2$ was increased 10 mm Hg in five patients over a 10-minute period. Under baseline conditions, there was no difference in arterial blood pressure, blood gas levels, or brain temperature between patients who underwent temporary arterial occlusion or those in whom hypercapnia was induced. In patients in whom hypercapnia was induced, H^+ , PCO_2 , and HCO_3^- concentrations increased and all values returned to baseline levels within 10 minutes. In 10 patients who underwent a median 9-minute arterial occlusion, transient ischemia was seen with an increase in tissue H^+ and PCO_2 levels of 100% and 60%, respectively, and a 20% decrease in HCO_3^- levels. After a 10-minute postischemic recovery, only PCO_2 had returned to baseline levels. These results are consistent with a rapid equilibration of lactic acidosis across the cell membrane during ischemia which decreases HCO_3^- concentration. After ischemia, extracellular acidosis may be prolonged because of the extrusion of H^+ from the cell by membrane ion exchange.

Key Words * ischemia * hydrogen ion * carbon dioxide * bicarbonate * aneurysm clipping

During cerebral ischemia, brain tissue H^+ concentration is stable until tissue blood flow falls to 35 $ml \cdot 100 g^{-1} \cdot min^{-1}$, below which it increases markedly.[6,14] Anaerobic metabolism initiated by ischemia induces lactic acidosis and elevated tissue PCO_2 . [9,10, 19] However, it is unclear whether the extracellular HCO_3^- concentration is decreased.[20,22] After an ischemic episode, extended tissue acidosis may contribute to neuronal injury, but the changes in tissue acid base during this period are not clear.[18,20] It is also not understood how ischemic changes in tissue acid base reported in animal models relate to temporary ischemia in humans. We have measured brain tissue acid base changes during an ischemic insult produced by occlusion of a middle or anterior cerebral distribution artery in patients undergoing craniotomy for cerebrovascular surgery. These changes were compared with a control group

of patients in whom respiratory acidosis was induced by artificially decreasing ventilation.

CLINICAL MATERIAL AND METHODS

Patient Population

Eighteen patients undergoing craniotomy for cerebrovascular surgery were evaluated. Tissue gas levels and H^+ concentrations were measured during arterial occlusion to facilitate aneurysm clipping in 12 patients or arteriovenous malformation resection in one patient. In five other patients, $PaCO_2$ was increased by 10 mm Hg as a control treatment for cerebral arterial occlusion. These studies were approved by the institutional review board for clinical research and informed consent was received.

Surgical Procedure

Patients were anesthetized with 10 to 15 $\mu\text{g/kg}$ fentanyl and 3 to 5 mg/kg thiopental; they were paralyzed with 100 $\mu\text{g/kg}$ vecuronium, intubated, and ventilated with 0.8% end-tidal isoflurane. The fraction of inspired O_2 was 0.4 and $PaCO_2$ was maintained between 30 and 35 mm Hg. Esophageal temperature was allowed to decrease to 35°C . A radial artery catheter was inserted to measure arterial pressure and to obtain arterial blood gas samples. Electroencephalographic (EEG) recordings were made using electrodes placed on the skin over the forehead. (model A1000 EEG monitor; Aspect, Boston, MA). A craniotomy was performed and the dura was retracted.

Intraoperative Monitoring

A probe (Paratrend 7 sensor; Biomedical Sensors, High Wycombe, UK) was inserted 4 cm into the cortex in all patients. The sensor probe was inserted into tissue within the arterial distribution at risk for ischemia during cerebral arterial occlusion. The sensor is supplied as a sterile, disposable device composed of two modified optical fibers for the measurement of PCO_2 and H^+ , and a thermocouple for the determination of temperature. The outer surface of the sensor has a covalently bonded heparin coating. The pH and PCO_2 sensors are separated by 1 cm at the end of the probe, which is 0.5 mm in diameter. The void between the sensors is filled with acrylamide gel containing phenol red. Changes in H^+ concentration produce color changes in phenol red, which can be detected by the H^+ fiberoptic element. The CO_2 sensor includes an ion impermeable barrier that excludes the movement of H^+ but allows the movement of CO_2 . Inside the barrier, CO_2 alters the local H^+ , producing a color change in phenol red that is detected by the CO_2 fiberoptic elements. The PCO_2 and H^+ measurements were corrected for local temperature to 37°C . Tissue HCO_3^- was calculated from PCO_2 and pH measurements using the Henderson-Hasselbalch equation.[3]

The sensor is packaged with a tonometer containing buffer solution that serves as a calibrating medium. Before the sensor was inserted into the patient it was calibrated with precision gases supplied with the monitor. The CO_2 and pH calibration curves are constructed within the range of 10 to 80 mm Hg and 6.80 to 7.80, respectively, using the three CO_2 gas concentrations: 2%, 14 mm Hg (pH = 7.83); 5%, 36 mm Hg (pH = 7.43); and 10%, 71 mm Hg (pH = 7.13). The range and 95% confidence interval limits for each sensor were determined in in vitro testing: CO_2 range, 10 to 80 mm Hg, 95% confidence limits ± 3 mm Hg; and pH range, 6.80 to 7.80, 95% confidence limits ± 0.03 . The 0 to 90% response time for each sensor was: CO_2 , 143 seconds and pH, 78 seconds.

After a 30-minute equilibration period, baseline measures of end-tidal CO₂ and anesthetic gas levels (Datex Instruments, Helsinki, Finland), mean arterial pressure (MAP), blood and brain tissue PCO₂, H⁺, and temperature were recorded. Arterial blood pressure, end-tidal gas levels, and tissue data were collected by computer using Labview (National Instruments, Dallas, TX) every 10 seconds.

Protocol Response

In patients undergoing occlusion, etomidate (0.2-0.4 mg/kg) was given to induce a burst suppression EEG response before the temporary clip was placed. After 3 to 5 minutes of burst suppression EEG activity, a temporary clip was placed on the middle cerebral artery (MCA) in 10 patients or the anterior cerebral artery (ACA) in three. The changes in tissue gas levels, H⁺, and HCO₃⁻ were measured during arterial occlusion and for a 10-minute recovery period.

In five patients, steady-state baseline values were obtained for arterial blood gas levels, MAP, and tissue PO₂, PCO₂ and H⁺, and then the ventilation rate was decreased to increase PaCO₂ 10 mm Hg over a 10-minute period. The PaCO₂ was then returned to baseline levels. In both treatment groups, end-tidal isoflurane was constantly maintained during the experiment.

Statistical Analysis

Data are reported as the mean ± standard deviation. Baseline MAP, arterial blood and tissue PCO₂, H⁺, and HCO₃⁻ were compared between the groups using t-tests. Changes in tissue PCO₂, H⁺, and HCO₃⁻ during arterial occlusion were compared to baseline measurements within each group using repeated-measures analysis of variance and paired t-tests used for post hoc comparisons. A Pearson Product Moment correlation was calculated using the change in H⁺ produced by ischemia and the H⁺ concentration at the end of the recovery period.

TABLE 1 BASELINE MAP, PAO ₂ , PACO ₂ , PH, AND BRAIN TEMPERATURE LEVELS IN PATIENTS IN WHOM AN INCREASE IN ARTERIAL CO ₂ OR ISCHEMIA WAS PRODUCED*						
Group	No. of Patients	MAP (mm Hg)	PAO ₂ (mm Hg)	PACO ₂ (mm Hg)	pH	Brain Temp (°C)
hypercapnia	5	82 ± 15	176 ± 41	32 ± 4	7.4 ± 0.05	36 ± 0.8
ischemia	10	81 ± 11	185 ± 60	33 ± 4	7.41 ± 0.04	35.4 ± 1.6
* Data are expressed as the mean ± standard deviation. apH = arterial pH.						

RESULTS

Under baseline conditions there was no significant difference in arterial blood pressure, blood gas levels, and pH and brain temperature between patients who received a CO₂ challenge and those in whom a cerebral artery was occluded (Table 1). Three patients in whom an artery was clipped were not included in the analysis. Two of these patients did not show ischemic changes during temporary ACA occlusion. In a third patient, an arterial clip that was placed to stop bleeding during AVM resection was not removed. Tissue pH decreased from 7.19 to 6.36 and tissue PCO₂ increased from 45 mm Hg to 145 mm Hg after the clip was placed. This patient developed seizures in the postoperative period and died on

postoperative Day 2. Other patients in whom a temporary artery clip was placed showed ischemic changes in tissue pH and PCO₂ and recovery when the clip was removed. An example of the changes in tissue PCO₂, H⁺, and HCO₃⁻ during arterial occlusion is shown in Fig. 1.

Fig. 1. Graph showing tissue H⁺, PCO₂, and HCO₃⁻ levels in a representative patient during MCA occlusion. Arterial clipping resulted in an increase in PCO₂ and H⁺ and a decrease in HCO₃⁻. After clip removal, PCO₂ returned to baseline levels, but there was a secondary decrease in HCO₃⁻ concentration. This was associated with a prolonged decrease in H⁺ concentration in the extracellular space.

Tissue PCO₂ and H⁺ increased simultaneously while HCO₃⁻ decreased during the period of occlusion. The PCO₂ decreased to baseline levels within 5 minutes after the occlusion; however, H⁺ remained elevated. After blood flow was reestablished, tissue HCO₃⁻ decreased below ischemic levels. A similar ischemic response was seen in the 10 patients who underwent occlusion for aneurysm clipping (Fig. 2).

Fig. 2. Bar graphs showing tissue PCO_2 , H^+ , and HCO_3^- levels during ischemia and 10 minutes after recovery from ischemia in nine patients. Ischemia was associated with an increase in PCO_2 and H^+ concentration and a decrease in HCO_3^- . Ten minutes after ischemia ceased, PCO_2 was not different from baseline, but H^+ was still increased and HCO_3^- was decreased compared with baseline levels.

The median time of temporary clipping was 9 minutes (range 2-35 minutes). Tissue H^+ and HCO_3^- did not return to baseline levels within the 10-minute recovery period after ischemia, and there was a significant correlation between the decrease in pH during ischemia and the pH in the recovery period ($r = 0.96$, $p < 0.001$). During the CO_2 challenge, PaCO_2 increased 10 ± 1 mm Hg in the five patients tested. Tissue PCO_2 , H^+ , and HCO_3^- increased and then returned to baseline levels within 10 minutes of recovery (Fig. 3).

Fig. 3. Bar graphs showing tissue PCO_2 , H^+ , and HCO_3^- levels during hypercapnia produced by a decrease in ventilation in five patients. Concentrations of PCO_2 , H^+ , and HCO_3^- increased during hypercapnia and returned to baseline levels 10 minutes after ventilation was returned to normal.

DISCUSSION

In this study we found that during hypercapnia there is a small but significant rise in brain tissue HCO_3^- concentration. This is consistent with previous studies that suggest that H^+ movement from the extracellular space or HCO_3^- movement in the opposite direction may occur during increases in tissue PCO_2 . [8,11] This may involve energy-requiring ion transport across the cell membrane because the increase in extracellular HCO_3^- is abolished by acidosis or hypoxia. In contrast to the CO_2 challenge, we found ischemia produced by temporary arterial occlusion resulted in an increase in H^+ and PCO_2 and a reduction of tissue HCO_3^- . In the recovery period, tissue PCO_2 returned to baseline levels; however, H^+ remained elevated and HCO_3^- was further reduced. This may be

caused by H^+ extrusion from the intracellular to the extracellular space as the neurons recover from the ischemic event.

Ischemic Acidosis

Kraig, et al.,[12] showed that excessive acidosis can kill neurons; they injected lactic acid into brain tissue and observed an infarction when extracellular pH was less than 5.30. In vitro studies have shown that extracellular acidosis produced by lactate

produces neuronal death more rapidly than HCl.[4] This is likely because of the ability of lactate to diffuse easily across the membrane barrier and decrease intracellular pH. Modest extracellular acidosis has produced a delayed cell death seen at 48 hours.[15] This is similar to delayed cell death seen after ischemia and is independent of glutamate activity. These results indicate that the onset time of neuronal death is related to the severity and the length of tissue acidosis.

It is possible that acid-sequestering mechanisms in glial cells protect neurons from H^+ -induced injury. In a rat model of complete ischemia, Kraig, et al.,[13] found that extracellular H^+ did not change, whereas lactate concentration increased to 15 to 17 mmol/kg. They suggested that maintenance of a constant extracellular H^+ concentration even while lactate is increasing is caused by H^+ accumulation by astroglia. However, this was not supported by Katsura, et al.,[10] who found a linear relationship between tissue PCO_2 , H^+ , and lactate in rats during ischemia. Because the rise they observed in PCO_2 and H^+ was directly related to the rise in tissue lactate, this does not support the presence of an acid-sequestering glial compartment. Our results do not speak directly to this issue because we did not measure lactate changes during the period of ischemia. However, the fact that PCO_2 and H^+ increased with the onset of ischemia in this study (Fig. 1) suggests that acid-sequestering mechanisms were not present.

Neuronal acidosis in the intracellular space may be attenuated during ischemia compared with the extracellular space. Nedergaard, et al.,[16] measured both extracellular and intracellular pH during MCA occlusion with a pH electrode and ^{14}C -methadione, respectively. At 1 hour of occlusion they found that extracellular pH decreased from 7.24 to 6.43, but that intracellular pH only decreased from 7.01 to 6.86. At 4 hours pH was 6.6 in both compartments. Insulin-induced hypoglycemia attenuated the decrease in extracellular pH, whereas hyperglycemia worsened it. This suggests that neurons can extrude H^+ into the extracellular space during the initial stages of ischemia, possibly by membrane ion exchange; however, other results do not support this. During 15 minutes of near-complete ischemia, Von Hanwehr, et al.,[22] reported that tissue PCO_2 increased from 45 to 149 mm Hg and lactate increased from 2 to 15 $\mu\text{mol/g}$. Extracellular pH decreased from 7.3 to 6.7 and intracellular pH decreased from 7.0 to 6.2. Intracellular HCO_3^- decreased from 10.5 to 5.2 $\mu\text{mol/g}$, but extracellular HCO_3^- did not change. They suggested that the greater decrease in intracellular compared to extracellular pH was due to a lack of equilibrium of lactate and H^+ movement between the intracellular and extracellular space. In a similar study, Smith, et al.,[20] found that brain tissue lactate increased to 10 $\mu\text{mol/g}$ and 20 $\mu\text{mol/g}$ in hypoglycemic and hyperglycemic rats, respectively, and extracellular pH decreased to 6.8 and 6.2, respectively, during incomplete ischemia. Tissue PCO_2 increased to 146 mm Hg (hypoglycemic) and 192 mm Hg

(hyperglycemic) and could be accounted for primarily by the decrease in intracellular HCO_3^- . Extracellular HCO_3^- decreased greater than $10 \mu\text{mol/g}$ in hyperglycemic but not in hypoglycemic rats during ischemia. They suggested that HCO_3^- transport from the intracellular to the extracellular space may explain the lack of change in extracellular HCO_3^- in hypoglycemic rats. Our measures indicate that extracellular HCO_3^- decreases even during short and modest ischemic events. This is consistent with previous studies that indicate there is a rapid equilibration of lactate across the cell membrane, which decreases intracellular and extracellular HCO_3^- . [15]

In addition to ischemic acidosis, we observed a postischemic period when extracellular acidosis was prolonged and HCO_3^- concentration did not recover, even as PCO_2 returned to baseline levels. This is consistent with studies showing that after status epilepticus or ischemia, intracellular pH returns to normal even though extracellular pH remains acidified. [18,20] This may occur in part due to metabolic acid consumption and to enhanced H^+ extrusion promoted by membrane ion pumps. It is not possible to evaluate the recovery of intracellular pH in our study. However, the transient decrease in extracellular HCO_3^- in the postischemic period suggests that it may occur at the expense of extracellular acidosis. A slower recovery of extracellular pH may occur because of H^+ or HCO_3^- exchange across the blood-brain barrier.

Acidosis in Relation to Other Parameters

The development of tissue acidosis has been related to other parameters such as cerebral blood flow (CBF), adenosine triphosphate (ATP), and ion homeostasis during ischemia. Using triple-barreled ion-sensitive electrodes to measure extracellular pH, K^+ , and Ca^{++} , Harris and Symon [6] found that pH began to decrease when CBF was decreased to 30 to $35 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ during bilateral carotid occlusion in rats. Marked acidotic shifts were seen when CBF decreased to $15 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ and extracellular K^+ simultaneously increased. A decrease in pH greater than 0.6 U was associated with rapid increases in K^+ and decreases in extracellular Ca^{++} . In baboons, Harris, et al., [5] measured tissue PO_2 , pH, and K^+ while CBF was decreased to ischemic levels by MCA occlusion combined with contralateral carotid constriction. The PO_2 decreased rapidly when CBF fell to $30 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ and pH fell when CBF decreased below $20 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Extracellular K^+ increased when CBF fell to $10 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Modest increases in K^+ were seen when pH decreased by 0.3 U and rapid increases in K^+ were seen when pH decreased 0.6 U . Obrenovitch, et al., [17] measured tissue ATP, pH, and lactate during MCA occlusion in baboons. Tissue pH did not change until CBF decreased below $30 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Decreases in pH to 6.25 occurred at a CBF of $20 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Sharp boundary zones were seen between low and normal pH, and brain tissue acidification was closely related to lactate accumulation and decreased ATP. These results indicate that when CBF is decreased to ischemic levels, tissue PO_2 decreases initially, followed by decreases in ATP and pH. When neuronal pH decreases more than 0.6 U , K^+ and Ca^{++} homeostasis are impaired.

Although exposure of neurons to critical levels of acidosis leads to cell death, modest decreases in tissue pH may attenuate injury by suppressing neuronal electrical and metabolic activity. [1,21] Nakai, et al., [14] simultaneously measured CBF, pH, and glucose metabolism using triple-tracer autoradiography during MCA occlusion in rats. They found that CBF, glucose metabolism, and pH were all lower in the ischemic region of hyperglycemic rats. This may be produced in part by an increase in K^+ conductance

and may be related to a decrease in the ATP/adenosine diphosphate ratio.[2] This is consistent with radiological studies showing that ischemia is associated with decreases in local neuronal metabolism.[7]

CONCLUSIONS

Studies suggest that enhanced neuronal damage is produced by ischemia when lactate approaches 18 to 20 $\mu\text{mol/g}$. [16] Marked decreases in PO_2 and pH occur at threshold CBF levels of 30 and 20 $\text{ml}\cdot 100\text{ g}^{-1}\cdot\text{min}^{-1}$, respectively, and loss of ionic homeostasis may occur at a CBF level of 10 $\text{ml}\cdot 100\text{ g}^{-1}\cdot\text{min}^{-1}$ when pH has decreased to approximately 6.6. Our results suggest that ischemic changes in tissue PCO_2 , H^+ , and HCO_3^- can be measured during ischemic events in patients. The magnitude of these changes may be used to predict the risk of ischemic neuronal injury and recovery of normal acid-base status after ischemia.

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