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Hypoxic Brain Tissue following Subarachnoid Hemorrhage

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Background: **Subarachnoid hemorrhage can lead to cerebral ischemia and irreversible brain injury. The purpose of this study was to determine whether subarachnoid hemorrhage produces changes in brain tissue oxygen pressure, carbon dioxide pressure, or pH during surgery for cerebral aneurysm clipping.**

Methods: **After institutional review board approval and patient consent, 30 patients undergoing craniotomy for cerebral aneurysm clipping were studied, 15 without and 15 with subarachnoid hemorrhage. Patients with subarachnoid hemorrhage were prospectively separated into groups with modest (Fisher grade 1 or 2; n = 8) and severe bleeds (Fisher grade 3; n = 7). After a craniotomy, a probe was inserted into cortex tissue supplied by the artery associated with the aneurysm. Baseline measures were made in the presence of a 4% end-tidal desflurane level. The end-tidal desflurane level was increased to 9% before clipping of the aneurysm, and a second tissue measurement was made.**

Results: **The median time of surgery after subarachnoid hemorrhage was 2 days, ranging from 1 to 13 days. During baseline anesthesia, brain tissue oxygen pressure was 17 ± 9 mmHg (mean ± SD) in control patients, 13 ± 9 mmHg in those with Fisher grade 1 or 2 hemorrhage, and 7 ± 6 mmHg in those with Fisher grade 3 hemorrhage ($P < 0.05$ compared with control). Brain tissue pH was 7.10 ± 0.10 in control patients, 7.14 ± 0.13 in those with Fisher grade 1 or 2 hemorrhage, and 6.95 ± 0.18 in those with with Fisher grade 3 hemorrhage ($P < 0.05$). At a 9% end-tidal desflurane level, brain tissue oxygen pressure increased to 19 ± 9 mmHg and brain tissue pH increased to 7.11 ± 0.11 in patients with Fisher grade 3 hemorrhage ($P < 0.05$ for both increases).**

Conclusion: **These results show that subarachnoid hemorrhage can significantly decrease brain tissue oxygen pressure and pH related to the severity of the bleed. Increasing the desflurane concentration to 9% increased brain tissue oxygen pressure in all patients and brain tissue pH in patients with subarachnoid hemorrhage with baseline acidosis. (Key words: Neurotrend; oxygen; pH.)**

SUBARACHNOID hemorrhage (SAH) can lead to cerebral ischemia and irreversible brain injury.[1-3] It is hypothesized that cerebral vasospasm, decreased cerebral blood flow, or loss of cerebrovascular regulation after SAH impairs brain tissue oxygenation.[4,5] In patients with SAH, investigators demonstrated jugular-bulb oxygen desaturation and related this to brain injury and death.[6,7] Direct measurement of brain tissue oxygen pressure (Pt_{O_2}) in individual patients with SAH or head injury in the intensive care unit show that if Pt_{O_2} decreases to less than 10 mmHg, it is associated with a poor neurologic outcome.[8] However, brain tissue studies of SAH have not been compared with a control group without SAH. The purposes of this study were to measure Pt_{O_2}, brain tissue carbon dioxide pressure (Pt_{CO_2}), and brain tissue pH (pHt) during surgery for clipping of cerebral aneurysm in patients with and without SAH, and to evaluate the response to increased desflurane concentration.[9,10]

Methods

These studies received University of Illinois Institutional Clinical Review Board approval, and informed consent was received from patients or family members. Patients were recruited who were undergoing craniotomy for clipping of cerebral aneurysms. These included 15 control patients who had not bled and 15 patients who had SAH 1-13 days before surgery (table 1). Fisher scores were determined before surgery by computerized tomographic scan: 1 = no blood observed, 2 = diffuse clots or layer less than 1 mm thick, 3 = blood layer more

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Table 1. Patient Demographics with and without Subarachnoid Hemorrhage

Group	Patient No.	Sex	Age	Aneurysm Location	Fisher Grade	Days Past Bleed
No bleed	1	F	38	R MCA		
	2	F	60	R PCA		
	3	F	48	L MCA		
	4	F	44	L MCA		
	5	M	57	L ICA		
	6	F	51	R PCA		
	7	F	56	R ACA		
	8	F	50	L MCA		
	9	F	66	L PCA		
	10	M	46	R ACA		
	11	M	43	L ICA		
	12	F	51	R ACA		
	13	M	62	L ACA		
	14	F	59	L MCA		
	15	F	69	L MCA		
Bleed	1	F	52	L MCA	3	1
	2	M	39	R ACA	3	2
	3	F	47	R MCA	2	5
	4	M	55	R PCA	1	2
	5	M	61	L MCA	1	3
	6	F	47	L ICA	3	2
	7	F	45	R MCA	2	13
	8	F	60	R MCA	2	2
	9	F	50	R MCA	1	2
	10	F	59	L ICA	2	3
	11	M	49	R ACA	3	2
	12	M	71	L MCA	3	3
	13	F	46	L ACA	3	2
	14	M	59	R ACA	3	2
	15	F	49	R MCA	2	10

ACA = anterior cerebral artery; F = female; ICA = internal carotid artery; L = left; M = male; MCA = middle cerebral artery; PCA = posterior cerebral artery; R = right.

than 1 mm thick. For this study, patients with Fisher grade 1 or 2 hemorrhaging were considered to have modest SAH (n = 8), and those with Fisher grade 3 to have severe SAH (n = 7).

Patients were anesthetized with 10-15 μg/kg fentanyl and 3-5 mg/kg thiopental and paralyzed with vecuronium, their tracheas were intubated, and their lungs ventilated with 4-6% desflurane in oxygen and air (inspired oxygen fraction = 0.4). Mean arterial pressure was measured continuously using a radial artery catheter, and esophageal temperature was allowed to decrease to 34°C during surgery. Arterial carbon dioxide tension was maintained at 30-35 mmHg, corrected to a temperature of 37°C.

After pterional craniotomy and dural retraction, a Neurotrend probe (Diametrics, St Paul, MN) that measures Pt_{O_2}, Pt_{CO_2}, pHt, and brain temperature was inserted 2 cm into cortex tissue supplied by the artery associated with the aneurysm. Probes placed for anterior cerebral artery aneurysms were close to the midline; probes for middle cerebral artery, posterior cerebral artery, and internal carotid artery aneurysms were more lateral, but all probes were placed in the frontal cortex. Probe placement for each artery was standardized and was not within the surgical field. The probe was covered to avoid extraneous light during the procedure, and care was taken to avoid retractor pressure in the region of tissue measurement. After a 30-min equilibration period with an end-tidal desflurane concentration of 4%, steady-state measurements of Pt_{O_2}, Pt_{CO_2}, *p*H, tissue temperature, and mean arterial pressure were obtained. All parameters were collected and averaged every 10 s by a computer using a Labview program (National Instruments, Dallas, TX).

Nine percent desflurane was requested by the neurosurgeon before clipping of the aneurysm.[9] The end-tidal desflurane level was maintained at 9% for 15 min, and blood pressure was maintained at 90-95 mmHg with an

Table 2. Mean Arterial Pressure, Arterial Oxygen Pressure, Carbon Dioxide Pressure, pH, Brain Temperature, Brain Tissue Oxygen Pressure, Carbon Dioxide Pressure, and pH in Control Patients and Patients with Subarachnoid Hemorrhage during Aneurysm Surgery

Group	n	End-tidal Desflurane	MAP (mmHg)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa	Br Temp (°C)	Pt_{O_2} (mmHg)	Pt_{CO_2} (mmHg)	pHt
No bleed	15	4%	86 ± 6	204 ± 41	33 ± 4	7.42 ± 0.04	35.1 ± 0.7	17 ± 9	52 ± 7	7.10 ± 0.10
		9%	92 ± 9				34.8 ± 1.0*	27 ± 14*	46 ± 5*	7.14 ± 0.12
Modest SAH	8	4%	87 ± 9	182 ± 27	32 ± 2	7.45 ± 0.04	36.1 ± 1.3	13 ± 9	54 ± 27	7.14 ± 0.13
		9%	91 ± 2				35.6 ± 1.7	24 ± 22*	51 ± 18	7.15 ± 0.18
Severe SAH	7	4%	85 ± 5	226 ± 71	33 ± 2	7.42 ± 0.03	35.3 ± 0.9	7 ± 6#	55 ± 10	6.95 ± 0.18#
		9%	93 ± 3				35.1 ± 0.9	19 ± 10*	48 ± 8*	7.11 ± 0.11*

Mean ± SD.

* = $P < 0.05$ compared to baseline.

† = $P < 0.05$ compared to control at same treatment.

Br Temp = brain temperature; MAP = mean arterial pressure; Pa_{CO_2} = carbon dioxide pressure; Pa_{O_2} = arterial oxygen pressure; pHa = pH; pH = pHt; Pt_{CO_2} = brain tissue carbon dioxide pressure; Pt_{O_2} = brain tissue oxygen pressure; SAH = subarachnoid hemorrhage.

intravenous phenylephrine infusion before the second tissue measurement in each patient. During this time no additional surgery was performed.

Statistical Analysis

Subarachnoid hemorrhages were separated prospectively into two groups: modest SAH (Fisher grade 1 or 2 [n = 8]) and severe SAH (Fisher grade 3 [n = 7]). Data are reported as the mean ± SD. Comparisons of cardiovascular and tissue measures among the three experimental groups at baseline and during 9% desflurane were made by analyses of variance. Baseline and 9% desflurane were compared within experimental groups using a two-way repeated measures analysis of variance. Tukey tests were used for *post hoc* testing if appropriate. If normality and equal-variance tests indicated that the data were not parametric, then Kruskal–Wallis analysis of variance on ranks was performed. Analyses were performed using Sigma Stat (SPSS, Chicago, IL).

Results

The most common aneurysm location was the middle cerebral artery, followed by the anterior cerebral artery in both experimental groups (table 1). The median time of surgery after SAH was 2 days, with a range of 1–13 days. During baseline anesthetized conditions, there was no difference in mean arterial pressure, arterial blood gases, or brain temperature between control patients and patients with SAH (table 2). During treatment with 9% desflurane, mean arterial blood pressure was maintained above 90 mmHg, and brain temperature decreased modestly.

During baseline conditions, Pt_{O_2} and pHt were lower in patients with Fisher grade 3 hemorrhage compared with controls (table 2). At a 9% desflurane concentration, Pt_{O_2} increased significantly in all patient groups. In patients with Fisher grade 3 hemorrhage, pHt increased with 9% desflurane to levels seen in controls. No aneurysm rupture occurred during treatment with 9% desflurane in any patient.

Discussion

We found that patients with SAH undergoing surgery for clipping of cerebral aneurysm have lower Pt_{O_2} and pHt levels compared with control patients, with a greater effect as the amount of hemorrhage increases. Control and SAH patients responded to 9% desflurane with an increase in Pt_{O_2}. In patients with Fisher grade 3 SAH, tissue hypoxia and acidosis recovered to control levels. These results indicate that brain ischemia after SAH is significantly related to the amount of hemorrhage. Tissue hypoxia and acidosis were reversed by treatment with 9% desflurane.

Progressive decreases in cerebral blood flow have been reported in patients with SAH for 3 weeks after hemorrhage, and the decrease in blood flow is related to a worsening in clinical grade.[1,2] Others report that cerebral blood flow is not altered within 7 days after SAH, but cerebral pressure autoregulation and cerebrovascular carbon dioxide reactivity are abnormal, and this dysfunction is correlated with clinical grade and development of cerebral vasospasm.[11,12] However, cerebrovascular carbon dioxide

reactivity is intact in other patients with SAH, and it has been questioned as a measure of pathology related to subsequent brain injury.[13] Although there is evidence of sequential ischemic cerebrovascular changes initiated by SAH, these results are controversial.[14] This may be related to the time of evaluation or the amount of blood associated with SAH, which are variable between studies.

Jugular-bulb oxygen saturation has been tested as an early indicator of cerebral ischemia after SAH. In 26 patients with SAH, jugular oxygen saturation was normal (0.56–0.74%) 90% of the time.[6] If jugular oxygen desaturation was seen, it was significantly correlated with increased intracranial pressure. Other investigators did not find a significant relation between low jugular oxygen saturation and the incidence of cerebral vasospasm.[7] However, SAH patients with low jugular-bulb oxygenation had a higher incidence of ischemic injury and death. These results indicate that jugular-bulb oxygenation can be intermittently low after SAH, and that this hypoxic effect is related to subsequent brain injury.

The measurement of Pt_{O_2} provides a more direct indication of local brain oxygenation than does jugular-bulb saturation. In studies of comatose patients with head injury and SAH, hypoxic episodes with Pt_{O_2} less than 10 mmHg were associated with unfavorable neurologic outcome.[5] In patients with SAH or head injury, brain tissue hypoxia was observed intermittently, even with normal cerebral perfusion pressure.[15] Interventions such as increasing cerebral perfusion pressure and decompressive craniotomy consistently increased brain oxygenation. Our results agree that low tissue oxygenation is present after SAH, although cerebral perfusion pressure is normal.

Previous studies suggest that the ability of 9% desflurane to increase Pt_{O_2} is related to an increase in cerebral blood flow and a decrease in brain metabolism.[16,17] High-dosage desflurane increases cerebral blood flow in dogs.[16] Increased Pt_{O_2} occurs simultaneously with an increase in laser Doppler measured brain blood flow during 9% desflurane in patients.[17] High-dosage desflurane abolishes autoregulation, and if blood pressure is not maintained above 90 mmHg, Pt_{O_2} decreases. This indicates that there is no direct effect of desflurane on the sensor to produce a falsely elevated Pt_{O_2} level. Other anesthetics that produce electroencephalographic burst suppression have different effects on Pt_{O_2}: Thiopental does not change tissue oxygenation, and etomidate is associated with a significant decrease in Pt_{O_2}.[9,17] The cerebrovasodilating effect of inhalation anesthetics may be important for the increase in Pt_{O_2} because we observed in dogs that a 3% end-tidal isoflurane concentration increases brain tissue oxygenation (unpublished results, July 1999).

We observed that 9% desflurane increased Pt_{O_2} in all groups, but an increase in pHt was more dependent on baseline acid–base status. This agrees with previous results that if pHt is 7.1 or higher, changes induced by 9% desflurane are small.[17] This is probably an indication that if normal acid–base balance is attained in brain tissue, an increase in cerebral perfusion with desflurane is of little consequence. In contrast, Pt_{O_2} does not appear to be controlled in the same manner as pHt, and oxygenation can increase with 9% desflurane even if Pt_{O_2} appears to be normal. Previously it was shown that Pt_{O_2} is more closely related to tissue perfusion than to pHt.[18] This is probably an indication that tissue oxygenation is dependent on oxygen delivery and capillary partial pressure of oxygen (P_{O_2}). In contrast, the diffusion coefficient of carbon dioxide from tissue to blood is 20 times greater than oxygen, and, therefore, acid–base balance can be maintained at a relatively low perfusion state. However, at ischemic tissue perfusion levels, metabolic acidosis produced by critically low Pt_{O_2} is accompanied by impaired carbon dioxide clearance. The ability of 9% desflurane to reverse hypoxia and acidosis in patients with SAH may be an indication that tissue perfusion is increased toward normal levels.

One concern in this study is that differences in tissue gases were related to the cortex region measured; for example, the anterior cerebral artery or the middle cerebral artery arterial supply. However, control patients and patients with SAH were well-matched with respect to aneurysm location. In addition, we saw no evidence for differences in Pt_{O_2} with respect to aneurysm location in control patients. Dings *et al.*[19] reported that Pt_{O_2} was 10 mmHg higher at the surface of the cortex, compared with 1 cm deeper. This should not be a factor in our study because the probe always was placed at the same depth in each cortex region. This supports the conclusion that differences in Pt_{O_2} and pHt between control patients and those with Fisher grade 3 hemorrhage were related to SAH rather than to probe location.

In conclusion, these results show that patients with SAH have tissue hypoxia and acidosis during aneurysm clipping related to the severity of the bleed. At a median time of 2 days after SAH, significant tissue hypoxia and acidosis were seen in patients with Fisher grade 3 SAH compared with patients without SAH. Nine percent desflurane, given before clipping of an aneurysm, increased Pt_{O_2} in all patients and increased pHt in patients with Fisher grade 3 hemorrhage to the level of that seen in controls.

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