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Cerebrovascular Adaptation to Prolonged Halothane Anesthesia Is Not Related to Cerebrospinal Fluid pH

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The purpose of this study was to evaluate the time-dependent effects of steady-state halothane anesthesia on cerebrovascular variables and their relationship to cerebrospinal fluid (CSF) *p*H. Eight mongrel dogs underwent a 7-h anesthetic, receiving halothane (1.0% end-tidal), O_2 (50%), and balance N_2. Cerebral blood flow (CBF) was measured by injection of radioactively labeled microspheres. CSF was sampled from the cisterna magna and cerebral venous blood from the superior sagittal sinus. Measurements were made at 2 h postinduction and hourly for 5 h thereafter. Total CBF at 2 h postinduction was 148 ± 36 ml·100 g^{-1}·min^{-1} and showed a significant decay over the subsequent 5 h to 70 ± 3 ml·100 g^{-1}·min^{-1}. Regional variations were noted, those areas with highest initial flows showing both a greater relative and absolute reduction in flow. Cerebral vascular resistance increased significantly (39%), as did mean arterial pressure (15%). CSF *p*H values remained constant throughout the experiment. Arterial blood acid–base physiology was also unchanged. Sagittal sinus P_{CO_2} increased significantly from 43 ± 4 to 49 ± 3 mmHg while sagittal sinus *p*H decreased from 7.31 ± 0.01 to 7.37 ± 0.02, consistent with the normalization of CBF. Cerebral metabolic oxygen consumption did not change significantly. The authors conclude that time-dependent changes in cerebrovascular parameters under prolonged steady-state halothane anesthesia are not due to changes in CSF *p*H and thus brain extracellular acid–base chemistry. (Key words: Anesthetics, volatile: halothane. Brain: blood flow. Cerebrospinal fluid: *p*H.)

HALOTHANE, ENFLURANE, AND ISOFLURANE have been shown to markedly increase cerebral blood flow (CBF).[1–7] This is associated with decreases in mean arterial pressure (MAP) and cerebral vascular resistance[8] and occurs within the early minutes of induction.[1] Although a cardiovascular adaptation to the effect of prolonged halothane anesthesia was demonstrated early,[9] some recent studies have described this adaptive phenomenon in the cerebrovascular system, showing a trend toward normalization of flow over time.

Boarini *et al.* reported that dogs exposed to halothane or isoflurane demonstrated a time-dependent decay of previously elevated CBF over a 7-h anesthetic and that this effect was independent of an inspired concentration equivalent to 1.0 or 1.3 MAC.[10] Albrecht *et al.*, in a goat model, showed that this CBF decay during halothane anesthesia occurs over a 2.5-h time period, despite pharmacologic alpha and beta blockade, indicating adrenergic recovery not to be a component in this process.[8]

The cerebral circulation normally is regulated by changes in Pa_{O_2}, arterial blood pressure, and Pa_{CO_2}. Theye and Michenfelder found that cerebral metabolic oxygen consumption (CMR_{O_2}) is decreased by halothane in a dose-dependent manner, with an increase in sagittal sinus P_{O_2} (Pss_{O_2}).[11] Thus, cerebral hypoxia, under halothane anesthesia, seems unlikely to occur, unless cardiovascular stability is not maintained. If hypoxia was present, flow would be expected to increase, if anything. Halothane depresses cerebral autoregulation, CBF becoming pressure dependent at 1.0 MAC (0.76%) in the goat and 1.0% (end-tidal) in the rhesus monkey.[12,13] By contrast, CBF remains responsive to changes in Pa_{CO_2} at these and greater halothane concentrations.[4,12,14,15]

Whether or not extracellular (*i.e.*, periarteriolar) brain hydrogen ion concentration singularly mediates Pa_{CO_2} induced CBF changes remains controversial.[16–18] However, as the cerebral vasculature maintains sensitivity to changes in Pa_{CO_2}, normalization of flow over time may be due to changes in cerebral extracellular acid–base chemistry, particularly in a chronic preparation. The purpose of this investigation was to evaluate the time-

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TABLE 1. Changes in Blood Flow, Vascular Resistance, and Oxygen Consumption in Total Brain as a Function of Time

Time after Anesthesia Induction	CBF (ml·100 g^{-1}·min^{-1})	CVR (mmHg·ml^{-1}·100 g·min)	CMR_{O_2} (ml·100 g^{-1}·min^{-1})
2 h	148 ± 36	0.86 ± 0.27	6.2 ± 0.7
3 h	102 ± 10	0.94 ± 0.12	5.2 ± 0.6
4 h	94 ± 7	1.12 ± 0.09	5.1 ± 0.7
5 h	90 ± 19	1.22 ± 0.27	5.3 ± 0.6
6 h	71 ± 5*	1.44 ± 0.14*	4.4 ± 0.4
7 h	70 ± 3*	1.42 ± 0.10*	4.6 ± 0.6

Values are means ± SEM. Significant difference from 2 h value: *$P < 0.05$.

dependent effects of steady state halothane anesthesia on cerebrovascular variables and their relationship to cerebrospinal fluid *p*H.

Methods

Eight mongrel dogs (weight, 14–20 kg) were anesthetized with halothane and air, intubated, and mechanically ventilated with an inspired gas mixture of halothane titrated to a mean ± SD steady state end-tidal concentration of 0.99 ± 0.01% (Medical Gas Analyzer®, Series 1100, Perkin-Elmer Corporation) in 50% O_2, and balance N_2. Pa_{CO_2} was maintained at 38 ± 2 mmHg. End-tidal CO_2 was monitored continuously by capnometer (Hewlett Packard 4710A®) and correlated with Pa_{CO_2}. Pancuronium, 0.1 mg/kg, was administered initially, and repeated as necessary (0.5 mg bolus) for immobility. Pulmonary arterial blood temperature as measured by PA catheter thermistor was maintained at 38° C by surface heating or cooling.

Regional cerebral blood flow (rCBF) was determined six times in each animal by a radioactive microsphere technique[19–22] with the use of carbonized 15 ± 5 μm spheres labeled with Ce^{141}, Gd^{153}, Sc^{46}, Sr^{85}, Nb^{95}, and Sn^{113} (New England Nuclear). The microspheres, approximately 1.3×10^6 in number for each flow determination, were injected into the cardiac left ventricle via a catheter inserted retrograde via the left femoral artery and positioned manometrically. Blood reference samples were obtained from catheters in the left femoral and brachial arteries at a withdrawal rate of 1.03 ml/min, beginning 30 s before microsphere injection and continuing 3.0 min after injection. At the completion of each experiment, the brain was removed and divided into regions. The amount of isotope in these regions of the brain, plus specimens from other organs, including stomach, liver, jejunum, kidney, left ventricle, right ventricle, paraspinous muscle, temporalis muscle, and thoracic spinal cord was determined by differential spectroscopy with the use of a scintillation spectrometer (Packard Auto-Gamma Scintillation Spectrometer®).

Systemic arterial pressure was monitored via the right brachial artery. Central venous (CVP), pulmonary arterial (PAP), and pulmonary artery wedge pressures (PAWP) were measured via a pulmonary artery catheter. Cardiac output (CO) was determined by thermodilution in triplicate. Sagittal sinus pressure (SSP) was measured from a catheter inserted through a burr hole into the mid-portion of the sagittal sinus and threaded 1 cm caudally.

Immediately preceding each blood flow measurement, arterial and sagittal sinus blood samples were analyzed for *p*H, P_{O_2}, P_{CO_2}, hematocrit, hemoglobin, and oxygen content (LEX-O_2-CON TL® co-oximeter, Lexington Instruments Corp.). CMR_{O_2} was estimated by multiplying total cortical cerebral blood flow by the difference between oxygen contents of the systemic arterial and sagittal sinus bloods. Cerebrovascular resistance (CVR) was calculated from the difference between MAP and SSP, divided by total brain CBF. Systemic vascular resistance (SVR) was calculated by dividing the difference between MAP and CVP by the cardiac output.

Via a midline occipito-cervical incision, the occiptal-C1 interspace was exposed. A 20-gauge Teflon® catheter was inserted approximately 1 cm into the cisterna magna and secured with one drop of cyanoacrylate for periodic aspiration of CSF. At sampling intervals, corresponding to microsphere injections, the catheter was cleared and CSF (0.5 ml) anaerobically apirated into glass syringes for immediate analysis of *p*H (*p*H/Blood Gas Analyzer Model 713®, Instrumentation Laboratory, Inc.).

A 2-h preparation time was allowed for all animals, the end-tidal halothane concentration being maintained at 1.0% during the entire experiment. All measurements were recorded and microspheres injected 2 h postinduction and at hourly intervals over the subsequent 5-h period.

Data were analyzed by regression analysis and by analysis of variance (general linear models procedure) to determine trends across all time periods. The Newman-Keuls test was performed for comparison between individual time periods. Statistical significance was assumed when $P < 0.05$. The blood flow measurements are reported at mean ± standard error of the mean in ml·100 g^{-1}·min^{-1}.

Results

The initial measurements made after 2 h of steady state halothane anesthesia showed total CBF to be 148 ± 36 ml·100 g^{-1}·min^{-1}, decreasing by 52% to 70 ± 3 ml·100 g^{-1}·min^{-1} over the subsequent 5-h period ($P < 0.01$). Cerebral vascular resistance increased significantly (39%), corresponding to the reduction in flow (table 1, fig. 1). CMR_{O_2} was calculated at 2 h to be 6.2 ± 0.7 ml·100 g^{-1}·min^{-1} (mean ± SEM) and did not

change significantly, despite a calculated 26% decrease to 4.6 ± .5 ml·100 g^{-1}·min^{-1} 5 h later. Sagittal sinus pressure (SSP) remained nearly constant, despite a 52% reduction in flow.

A marked regional variation was seen, although all regions showed a pattern of decreasing blood flow over time (table 2). Linear regression analysis was performed on rCBF as a function of time. For each region, the slope of the rCBF decrease over time was plotted against the respective baseline rCBF (2 h postinduction), demonstrating that proportionate decay of rCBF is a function of the initial flow ($R^2 = 0.96$, $P < 0.001$), *i.e.* areas with higher initial flow showed a greater rate of decay in flow with time (fig. 2). This was true in both relative and absolute terms.

Hemodynamic changes are presented in table 3. MAP ($P < 0.005$) and PAP ($P < 0.04$) showed significant increases over time (15% and 14%, respectively). SVR showed no consistent trend for change. Heart rate, CVP, PAWP, and hemoglobin concentrations were unchanged. Myocardial and splanchnic blood flow showed no systematic variation over time.

Arterial P_{O_2}, P_{CO_2}, and *p*H remained stable. Pa_{O_2} was maintained at 235 ± 1 mmHg and Pa_{CO_2} at 38 ± 1 mmHg. There was no metabolic acidosis and the arterial bicarbonate ion concentration remained unchanged (table 4). Sagittal sinus p_{CO_2} increased with time ($P < 0.002$), corresponding to decreasing flow. This was accompanied by a decrease in sagittal sinus *p*H ($P < 0.005$).

Cerebrospinal fluid *p*H remained unchanged during the experiment (table 4). Linear regression analysis revealed no relationship between CSF *p*H and flow in any of the regions studied. CSF *p*H did vary as a function of both arterial and sagittal sinus *p*H ($P < 0.002$).

Discussion

Both halothane and isoflurane have been demonstrated to cause initial increases in CBF, followed by a trend for normalization of flow over several hours time.[8,10] Our study confirms the presence of this phenomenon during halothane anesthesia in the dog. In addition, we find that regions with higher initial flows show a greater per cent decline in flow over time than do those areas with less flow.

Cerebral blood flow is normally independent of cerebral perfusion pressure (MAP-ICP), being held constant as a function of changes in cerebrovascular resistance. Halothane anesthesia attenuates or abolishes this autoregulation in clinical doses.[12,13] Through myocardial depression and perhaps decreased SVR,[9] an initial reduction in MAP often occurs. The increase over time in MAP seen in the current animals might be expected to increase CBF. However, CBF actually decreased and the trend toward normalization of flow may have been attenuated by the recovery in MAP. This is supported by Albrecht *et al.*, who showed a persistent loss of

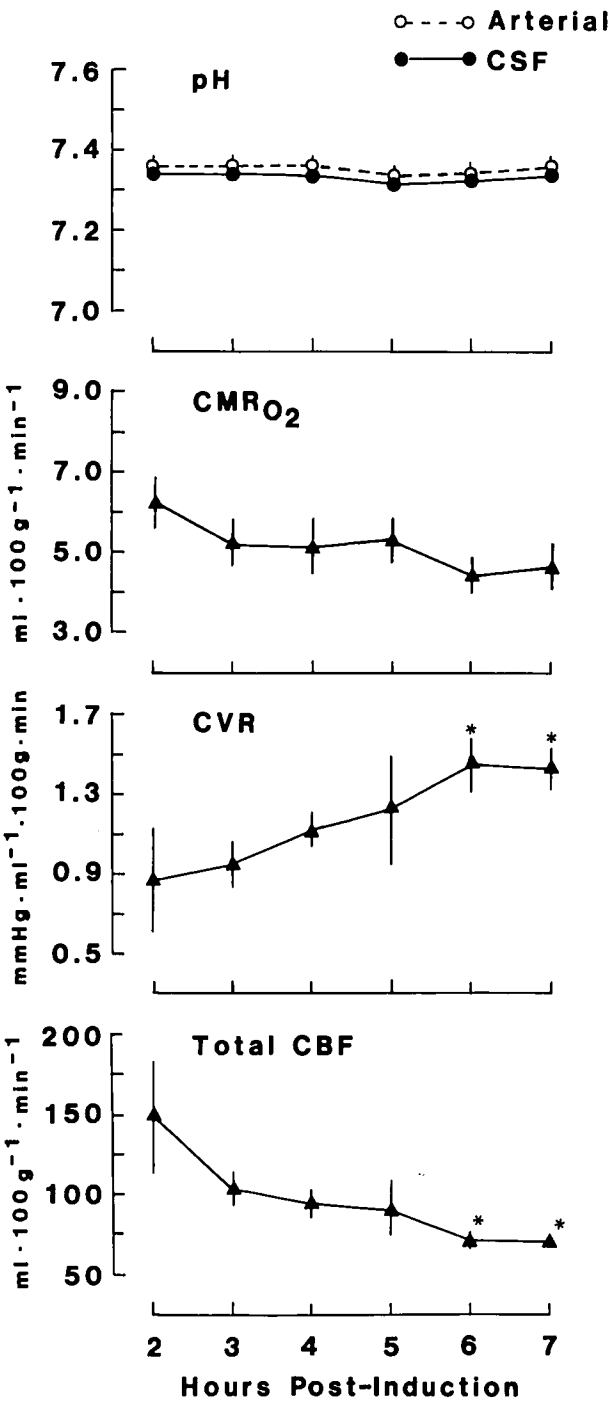

FIG. 1. Physiologic and metabolic values during steady state halothane anesthesia as a function of time. Initial measurements were taken at 2 h after halothane anesthesia induction. Values are means ± SEM at intervals (hours) after anesthesia induction. Significance difference from 2 h value: *$P < 0.05$.

TABLE 2. Regional Cerebral Blood Flow (ml·100 g^{-1}·min^{-1}) with End-tidal Halothane Maintained at 1.0 ± 0.01% as a Function of Duration of Anesthesia. Initial Measurements Taken at 2 h Postanesthesia Induction

	Regional CBF at Hourly Intervals after Anesthesia Induction					
	2 h	3 h	4 h	5 h	6 h	7 h
Total brain	148 ± 36	102 ± 10	94 ± 7	90 ± 19	71 ± 5*	70 ± 3*
Cerebral hemispheres	158 ± 39	108 ± 11	93 ± 6	97 ± 26	72 ± 4*	72 ± 3*
Total cortical gray	189 ± 47	126 ± 17	105 ± 7	115 ± 7	81 ± 5*	81 ± 4*
Frontal gray	210 ± 49	146 ± 19	119 ± 9	126 ± 44	83 ± 5*	82 ± 7*
Temporal gray	175 ± 41	112 ± 15	93 ± 7	103 ± 31	76 ± 6*	72 ± 3*
Parietal gray	189 ± 55	125 ± 18	109 ± 31	109 ± 31	77 ± 5*	75 ± 3*
Occipital gray	183 ± 40	127 ± 18	111 ± 11	113 ± 35	87 ± 7*	92 ± 9*
Corpus callosum	36 ± 8	30 ± 5	29 ± 2	27 ± 8	23 ± 3	20 ± 2
Caudate nucleus	255 ± 76	159 ± 13	148 ± 10	119 ± 24	101 ± 8*	102 ± 7*
Brain stem	68 ± 13	51 ± 2	52 ± 3	60 ± 14	47 ± 4	45 ± 2
Cerebellum	117 ± 26	80 ± 9	83 ± 6	87 ± 19	74 ± 9	71 ± 6
Cervical spinal cord	44 ± 9	27 ± 2	31 ± 4	33 ± 12	31 ± 7	26 ± 3

Values are means ± SEM.

* Significantly different from 2h value ($P < 0.05$).

cerebral autoregulation to rapid increases in MAP, despite a time-dependent decay in CBF.[8]

Previous studies of the phenomenon of cerebrovascular adaptation have measured inspired anesthetic gas concentrations.[8,10,23] Thus, the question remains if progressively deeper levels of anesthesia over time are associated with reduction in CBF. Indeed, Turner *et al.*, in a similar model with 1.0% inspired isoflurane found a gradual reduction in the voltage amplitude of the electroencephalogram recording over 4.5 h, which may have indicated a deepening level of anesthesia. Assuming that the end-tidal halothane partial pressure consistently reflects that of the brain parenchyma following initial uptake and distribution,[24] the present study controlled for this variable demonstrating that increasing anesthetic concentrations are not a factor in the adaptive mechanism.

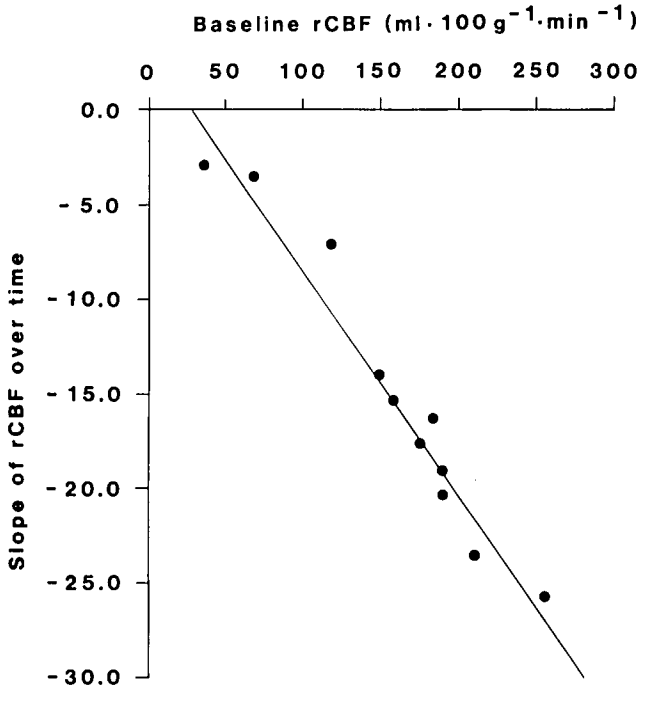

FIG. 2. In this figure, each point represents a region of the brain (see table 2). The abscissa depicts the baseline rCBF in ml·100 g^{-1}·min^{-1} (at 2 h postinduction, see text). The ordinate represents the slope of the rCBF decrease as a function of time for the respective region. As can be seen, a high initial rCBF leads to a greater reduction of rCBF over time. y = 3.58 − 0.12 (baseline rCBF), R^2 = 0.96, $P < 0.001$.

Spontaneous fluctuations in cerebral extracellular acid–base chemistry were considered possible in our preparation with a decreasing CBF and constant Pa_{CO_2}. The relevance of measuring CSF *p*H to reflect extracellular (*i.e.*, periarteriolar) values warrants discussion. The CSF is buffered exclusively by bicarbonate ion. Although formation of carbonic acid in the CSF occurs in the absence of carbonic anhydrase, the rate is slow. CSF and extracellular hydrogen ion and bicarbonate ion concentrations are equilibrated under steady state conditions, being a function of either diffusion or active transport of these ions.[25,26] A lag time for equilibration between the CSF and ECF is expected and may amount to approximately 30 min. Thus, a 30-min phase shift between CBF and CSF *p*H determinations would be expected. However, as the measured CSF *p*H remained unchanged the above effect was negligible in our preparation.

Reduction in CBF as a function of time also has been noted in awake immobilized preparations.[15,27] Takeshita *et al.*[27] found in three dogs a time dependent decay of CBF (35% reduction from control after 3 h). This effect

TABLE 3. Physiologic Variables as a Function of Time

	Physiologic Variables at Intervals after Anesthesia Induction					
	2 h	3 h	4 h	5 h	6 h	7 h
HR (beats/min)	124 ± 2	124 ± 8	128 ± 6	133 ± 3	129 ± 3	128 ± 7
MAP (mmHg)	88 ± 3	92 ± 1	101 ± 5	101 ± 4*	102 ± 5*	103 ± 5*
CO ($l \cdot min^{-1}$)	2.8 ± 0.3	3.3 ± 0.4	3.0 ± 0.3	3.8 ± 0.4	3.5 ± 0.5	3.1 ± 0.4
SVR ($mmHg \cdot l^{-1} \cdot min$)	31 ± 5	28 ± 3	35 ± 5	28 ± 4	32 ± 5	36 ± 6
PAP (mmHg)	15 ± 1	15 ± 1	16 ± 1	19 ± 1*	19 ± 1*	18 ± 1*
Temp (° C)	38.3 ± 0.4	38.3 ± 0.2	38.4 ± 0.3	38.0 ± 0.4	38.4 ± 0.3	38.5 ± 0.3
Hgb (g/dL)	12.7 ± 1.0	11.1 ± 1.1	11.4 ± 1.2	12.3 ± 2.0	12.2 ± 2.2	12.2 ± 2.1
Pa_{O_2} (mmHg)	239 ± 2	244 ± 6	241 ± 6	225 ± 4	234 ± 3	228 ± 5
Pss_{O_2} (mmHg)	53 ± 5	58 ± 4	53 ± 1	54 ± 6	51 ± 6	49 ± 4

Values are means ± SEM.

Significant difference from 2 h value: *$P < 0.05$.

was attributed to initial cerebral vasodilation in response to major surgical manipulation. Raichle *et al.*,[15] in a less invasive procedure (Kr^{85} clearance), found a time-dependent decrease of flow in awake animals, suggesting a time correction factor of 6% from baseline per hour. In the present study, this would yield a 30% decrease in flow, but a 52% decrease in flow was measured. Hence, an unexplained decrease of 22% after 5 h remains, when the effect of immobilization is considered. However, if this phenomenon is real, it is not manifested by derangements in blood acid–base or CSF *p*H values.

CMR_{O_2} showed a 26% decline over time, although this was not statistically significant. The initial value, 6.2 ± 0.7 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ was higher than expected in the dog receiving 1.0% end-tidal halothane. This may be elevated artifactually, representing a mismatch between regions where flow and CMR_{O_2} were measured, but is more likely due to the large variability in the initial CBF measurements and small sample size. A decreasing CMR_{O_2} would be expected in this model, however, as the A-V O_2 content difference remained relatively constant while flow decreased.

Of note, MAP underwent a highly significant (15%) increase over time similar to that reported by Albrecht *et al.*[8] This was not accompanied by an increase in SVR, although Eger *et al.*[9] found evidence for recovery from myocardial depression during halothane anesthesia in humans. A relative hypotension frequently was seen during the early stages of our experimental protocol and may have triggered a vasoconstricting response from the renin-angiotensin axis or vasopressin. Determination of these values may warrant further investigation as well as measurement of CBF over time while MAP is held constant in the normal range.

In conclusion, canine CBF showed a time-dependent decay under prolonged halothane anesthesia and a greater reduction in flow in regions with higher initial flows. This was not an effect of deepening levels of anesthesia over time, or acid-base phenomena.

The clinical relevance of this adaptation can be seen in neuroanesthetic practice if data from the dog can be extrapolated to humans. In cases where halothane is administered to promote cerebrovascular dilation (*e.g.*, carotid endarterectomy) the maximal effect will be achieved early in the anesthetic. In cases where brain hyperemia is to be avoied (*e.g.*, cerebral aneurysm clipping), halothane, if administered, should be instituted as early as possible, allowing for adaptive reduction in

TABLE 4. Acid–base Parameters during Prolonged Halothane Exposure at Hourly Intervals after Anesthesia Induction

	Arterial			Sagittal Sinus			
Hours	P_{CO_2} (mmHg)	*p*H	HCO_3^- (mEq/l)	P_{CO_2} (mmHg)	*p*H	HCO_3^- (mEq/l)	CSF *p*H
2	38 ± 2	7.36 ± 0.02	20 ± 2	43 ± 4	7.31 ± 0.01	21 ± 2	7.34 ± 0.01
3	36 ± 1	7.36 ± 0.02	19 ± 2	44 ± 1	7.32 ± 0.01	21 ± 2	7.34 ± 0.01
4	37 ± 1	7.36 ± 0.02	19 ± 2	47 ± 1	7.30 ± 0.02	21 ± 2	7.33 ± 0.01
5	41 ± 1	7.33 ± 0.03	20 ± 2	51 ± 1*	7.27 ± 0.02*	22 ± 2	7.32 ± 0.01
6	39 ± 1	7.34 ± 0.03	19 ± 2	50 ± 2*	7.27 ± 0.02*	21 ± 2	7.32 ± 0.01
7	38 ± 1	7.36 ± 0.02	20 ± 1	49 ± 3*	7.27 ± 0.02*	22 ± 2	7.34 ± 0.01

Values are means ± SEM.

Significant difference from 2 h value: *$P < 0.05$.

flow, thereby minimizing the brain retractor pressure required for surgical exposure.

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