# Cerebrospinal Fluid pH and $P_{CO_2}$ Rapidly Follow Arterial Blood pH and $P_{CO_2}$ with Changes in Ventilation

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**CHANGES IN VENTILATORY rate affect arterial blood pH and $P_{CO_2}$ within seconds to minutes, but the corresponding acute changes for cerebrospinal fluid (CSF) pH and $P_{CO_2}$ have not been as well documented. Using our previously-described swine model of brain retraction ischemia, we examined changes in arterial and CSF pH and $P_{CO_2}$ with acute changes in ventilation in four animals. Newly developed fluorescent dye technology permitted near-instantaneous recording of CSF pH and $P_{CO_2}$ during acute hyperventilation (end-tidal $P_{CO_2}$ of 20 mm Hg) and acute hypoventilation (end-tidal $P_{CO_2}$ of 50 mm Hg). The Puritan-Bennett 3300 Intra-Arterial Blood Gas Monitor (PB3300) was used with the sensor placed in the CSF in the interhemispheric fissure posterior to the corpus callosum. The following data were gathered at 5, 15, 30, and 60 minutes after the ventilatory change: arterial pH and $P_{CO_2}$, end-tidal $CO_2$, laser-Doppler cerebral blood flow, and CSF pH and $P_{CO_2}$. The baseline (normoventilation) values for arterial and CSF pH and $P_{CO_2}$ in swine were comparable to those in humans: arterial pH 7.44 and $P_{CO_2}$ 43 mm Hg; CSF pH 7.31 and $P_{CO_2}$ 55 mm Hg. Changes in pH and $P_{CO_2}$ with hyperventilation and hypoventilation occurred rapidly in both arterial blood and CSF. Steady-state values were reached within 15 minutes for hypoventilation, and 30 minutes for hyperventilation. The correlation between arterial and CSF values for both pH and $P_{CO_2}$ at 5, 15, 30, and 60 minutes were all very highly significant ($P < 0.001$) except for arterial and CSF $P_{CO_2}$ at 5 minutes ($P < 0.01$). CSF pH and $P_{CO_2}$ follow arterial blood gas pH and $P_{CO_2}$ rapidly with acute changes in ventilation. These results are consistent with previous research, and indicate the PB3300 may be useful in monitoring CSF pH and $P_{CO_2}$.** (Neurosurgery 34:466–470, 1994)

Key words: Acid-base equilibrium, Blood gas analysis, Cerebrospinal fluid, Hyperventilation, Hypoventilation

Changes in the pH and $P_{CO_2}$ of cerebrospinal fluid (CSF) are of clinical importance acutely (seconds to minutes), in the evaluation of brain death, subacutely (hours to days), in the use of hyperventilation to control brain swelling (e.g., in head trauma), and chronically (months to years), in adaptation to high terrestrial altitudes. Changes in ventilatory rate affect arterial blood pH and $P_{CO_2}$ within seconds to minutes, but the corresponding acute changes for CSF with changes in ventilation have not been as well established. Newly developed fluorescent dye technology permitted near-instantaneous recording of CSF pH and $P_{CO_2}$ during acute changes in ventilation (hyperventilation and hypoventilation) in our previously described large animal model for simulating intraoperative brain retraction.

## MATERIALS AND METHODS

The large animal model and surgical procedures have been described in detail (2, 3). The research protocol was approved by the appropriate committees of the Veterans Affairs Medical Center, Palo Alto, California. This study involved four juvenile swine: one was used to determine the feasibility of monitoring CSF pH and $P_{CO_2}$ during acute ventilatory changes, and three (all female; weight, 33–37 kg) for obtaining the data reported below.

After endotracheal intubation, anesthesia was maintained with isoflurane (Forane, Anaquest, Madison, WI) 1.5% to 2%. Femoral arterial and venous access were established by cut-down, and the head was placed in a stereotactic holder. Isotonic intravenous fluids were given at 2 ml/kg/h. A wide bilateral craniectomy was performed, as described previously (3).

For placement of the catheter to monitor CSF pH and $P_{CO_2}$, the posterior dural incision used previously in this animal model for stereotactic section of the corpus callosum was employed (2). This was a 2-mm incision 2 mm lateral to the midline approximately 6 cm posterior to the frontal poles. The sensor for the Puritan-Bennett 3300 pH/blood gas monitor

(Puritan-Bennett Corporation, Carlsbad, CA) was held vertically by a stereotactic tower above the dural incision. The 20-gauge intravascular catheter supplied with the sensor for radial artery cannulation was placed over the sensor tip prior to lowering the sensor through the dural incision. The catheter was advanced together with the sensor until a depth of 2.5 cm from the dural surface was reached, that is, immediately posterior to the splenium of the corpus callosum. The catheter was withdrawn and secured to the sensor with its Luer connector. Thus, 2.5 cm of the sensor tip was exposed to the intradural (interhemispheric) compartment, that is, the catheter covered the sensor from immediately subdural up to the sensor base at the Luer connector.

The following parameters were monitored continuously:

1. mean arterial blood pressure, electrocardiogram, heart rate, respiratory rate (using the Hewlett-Packard Model 78353B, Hewlett-Packard Corporation, Palo Alto, CA);
2. end-tidal $CO_2$ (using the SpaceLab Surgical Monitor 90603A, SpaceLab, Inc., Redmond, WA);
3. Cerebral blood flow (CBF) (using the Laserflo BPM-403A Blood Perfusion Monitor, Vasamedics, St. Paul, MN) with a needle point probe (0.8 mm in diameter) held by a stereotactic tower placed to contact the dura lightly in the posterior frontal region (3); and
4. CSF pH and $P_{CO_2}$ (using the Puritan Bennett 3300 pH/blood gas monitor).

Arterial blood gases, analyzed on standard hospital laboratory equipment (CIBA-Corning Model 278 Blood Gas System, CIBA-Corning Corporation, Medfield, MA), were obtained repeatedly as noted below. At the completion of the experiment, each animal was killed by intravenous injection of Beuthanasia-D (Schering-Plough Animal Health Division, Kenilworth, NJ).

For normoventilation, the ventilatory rate was adjusted to yield an end-tidal $CO_2$ of approximately 35 mm Hg (Table 2). The respiratory rate was usually in the range of 9 to 12 per minute. For hyperventilation, the respiratory rate was increased (usually to 20–26 per minute) to yield an end-tidal $CO_2$ of approximately 20 mm Hg (Table 2). For hypoventilation, the respiratory rate was decreased (to 8 per minute) to yield an end-tidal $CO_2$ of approximately 50 mm Hg (Table 2). These conditions were maintained for 60 minutes, with arterial blood pH and $P_{CO_2}$, CSF pH and $P_{CO_2}$, and CBF being recorded at 5, 15, 30, and 60 minutes.

## RESULTS

Comparison normoventilation values in humans and swine for pH and $P_{CO_2}$ in arterial blood and in CSF are given in *Table 1*. Although the pH of swine arterial blood (7.44) was slightly lower than the mean pH for swine (7.48) reported by Hannon et al. (10), their swine were less mature (weight, 20–25 kg), and their range for pH was 7.40 to 7.53. Our values were obtained during normoventilation under general endotracheal anesthesia rather than during spontaneous respiration.

**TABLE 1. Baseline Values in Humans and in Swine for Arterial Blood and Cerebrospinal Fluid pH and $P_{CO_2}$[a]**

| | pH | | $P_{CO_2}$ (mm Hg) | |
|---|---|---|---|---|
| | Blood | CSF[b] | Blood | CSF |
| Humans (n = 95) | 7.41 ± 0.01 | 7.33 ± 0.02 | 38 ± 2.3 | 48 ± 2.8 |
| Swine (n = 15) | 7.44 ± 0.04 | 7.31 ± 0.03 | 43 ± 6.4 | 55 ± 8.5 |

[a] **All values are the mean ± the standard deviation. Data for humans are from Table 1 of Posner et al. (17), a summary of their own data and those of four other studies. Data for swine are from the present study (data sets under normoventilation).**

[b] **CSF, cerebrospinal fluid.**

**TABLE 2. Respiratory Rate, End-Tidal $CO_2$, and Cerebral Blood Flow during Normoventilation, Hyperventilation, and Hypoventilation in Swine[a]**

| | Respiratory Rate (per min) | End-tidal $CO_2$ (mm Hg) | Cerebral Blood Flow (ml/100 g/min) |
|---|---|---|---|
| Normoventilation (min) | | | |
| 5 | 11.0 ± 1.7 | 36 ± 2.0 | 41 ± 4.2 |
| 15 | 10.5 ± 1.9 | 35 ± 4.6 | 39 ± 8.6 |
| 30 | 10.8 ± 2.5 | 35 ± 4.3 | 40 ± 7.3 |
| 60 | 11.3 ± 3.0 | 36 ± 1.0 | 44 ± 10.0 |
| Hyperventilation (min) | | | |
| 5 | 24.8 ± 3.6 | 27 ± 4.6 | 26 ± 4.6 |
| 15 | 25.0 ± 5.6 | 25 ± 4.9 | 28 ± 3.5 |
| 30 | 22.5 ± 4.9 | 20 ± 4.2 | 26 ± 0.7 |
| 60 | 21.0 ± 7.1 | 20 ± 2.1 | 29 ± 4.9 |
| Hypoventilation (min) | | | |
| 5 | 8.0 ± 0.0 | 49 ± 2.6 | 59 ± 9.3 |
| 15 | 8.0 ± 0.0 | 50 ± 2.1 | 56 ± 6.0 |
| 30 | 8.0 ± 0.0 | 51 ± 1.5 | 54 ± 6.7 |
| 60 | 8.0 ± 0.0 | 51 ± 1.5 | 58 ± 11.1 |

[a] **All values are the mean ± the standard deviation (n = 4, except for hyperventilation of 15 minutes (n = 3) and hyperventilation of 30 minutes and 60 minutes (n = 2 each).**

Values for respiratory rate, end-tidal $CO_2$, and CBF during normoventilation, hyperventilation, and hypoventilation are given in *Table 2*. It can be seen that the end-tidal $CO_2$ responded rapidly (i.e., at 5 minutes) to changes in ventilation, although somewhat more rapidly to hypoventilation than hyperventilation. The CBF followed the changes in ventilation as expected (rapid decrease with hyperventilation and increase with hypoventilation).

*Table 3* presents the values for pH and $Pco_2$ in arterial blood and CSF during hyperventilation and hypoventilation. With changes in ventilation, the changes in CSF pH and $Pco_2$ parallel those in arterial blood. Data from one of the trials are plotted in *Figure 1* for both hyperventilation (*Fig. 1A*) and hypoventilation (*Fig. 1B*).

The correlation coefficients between arterial and CSF values for both pH and $Pco_2$ at 5, 15, 30, and 60 minutes (combined hyperventilation and hypoventilation) were all highly significant ($r = 0.94$–$0.99$, $P < 0.001$), and were only less so for $Pco_2$ at 5 minutes ($r = 0.81$, $P < 0.01$) (4).

## DISCUSSION

In the 1960s, a substantial literature appeared on the relation between arterial blood and CSF pH and $Pco_2$. Reviews have been written by Davson (6) and Siesjo (20), and more recently by Leusen et al. (12) and Fishman (8). It was established that in the steady-state condition, the lumbar CSF pH is lower than the arterial blood pH (by 0.02–0.10 units), and the $Pco_2$ higher (by 4–11 mm Hg). Bicarbonate levels were found to be very similar in the CSF and arterial blood. Although not all studies are in agreement, it appears that cisternal CSF has a pH that is about 0.02 units less acidic and a $Pco_2$ that is about 3 mm Hg lower than those of the lumbar CSF (7, 16, 20). It was shown that cisternal CSF is more closely related than lumbar CSF to arterial blood during acute changes in acid-base status (7, 12).

Another finding from research in the 1960s is that cisternal CSF pH and $Pco_2$ follow arterial blood pH and $Pco_2$, both with changes in ventilation (hyperventilation) (7, 13) and with changes in the inspired $CO_2$ concentration (5, 11, 13). Fisher and Christianson (7) described the changes in the pH and $Pco_2$ of both arterial blood and CSF (cisternal *and* lumbar) in one subject who spontaneously hyperventilated for 10 minutes. The increase in pH and decrease in $Pco_2$ seen in the arterial blood after 10 minutes of hyperventilation were closely paralleled by changes in the cisternal (but not the lumbar) CSF pH and $Pco_2$. Lambertsen et al. (11), using anesthetized dogs undergoing both abrupt administration and abrupt withdrawal of inhaled $CO_2$ (7%), found that the pH changes in both arterial blood and CSF were exponential, with half times of less than 1 minute for arterial blood and approximately 5 minutes for CSF. Bradley et al. (5) used intubated, ventilated, anesthetized patients who were undergoing pneumoencephalography to study the effects of 5% $CO_2$ on arterial blood and cisternal CSF pH and $Pco_2$. The increase in arterial blood $Pco_2$ was more rapid than the increase in CSF $Pco_2$; they estimated that 20 to 30 minutes were needed for steady-state CSF $Pco_2$ to be reached after inhalation of 5% $CO_2$. Merwarth and Sieker (13) used intubated, ventilated, anesthetized dogs to study the effects of 10% $CO_2$ and marked hyperventilation (15 L/min) on arterial blood and CSF pH and $Pco_2$. Data were gathered at 2, 10, and 40 minutes after institution of hypercapnia or hypocapnia. Although steady-state was not reached even by 40 minutes, from their data, the changes in arterial blood pH and $Pco_2$ were more rapid than those in the CSF.

For subacute or chronic changes in CSF acid-base status, such as metabolic and respiratory acidosis and alkalosis in disease (8, 16) or adaptation to high altitude (19), consideration of CSF bicarbonate levels would be necessary. However, it has been shown that *acute* changes in CSF bicarbonate are small in

**TABLE 3. Arterial Blood and Cerebrospinal Fluid pH and $Pco_2$ during Hyperventilation and Hypoventilation in Swine[a]**

| | pH | | $Pco_2$ (mm Hg) | |
|---|---|---|---|---|
| | Blood | CSF[b] | Blood | CSF |
| Hyperventilation (min) | | | | |
| 0 | 7.40 ± 0.01 | 7.30 ± 0.01 | 47 ± 3.7 | 63 ± 9.9 |
| 5 | 7.52 ± 0.06 | 7.39 ± 0.03 | 31 ± 6.3 | 51 ± 10.0 |
| 15 | 7.58 ± 0.07 | 7.40 ± 0.08 | 29 ± 7.4 | 41 ± 7.5 |
| 30 | 7.63 ± 0.05 | 7.47 ± 0.09 | 23 ± 8.5 | 35 ± 8.5 |
| 60 | 7.65 ± 0.02 | 7.48 ± 0.04 | 23 ± 7.1 | 35 ± 11.3 |
| Hypoventilation (min) | | | | |
| 0 | 7.48 ± 0.03 | 7.31 ± 0.01 | 43 ± 3.2 | 51 ± 2.5 |
| 5 | 7.35 ± 0.03 | 7.24 ± 0.02 | 58 ± 4.5 | 63 ± 4.2 |
| 15 | 7.34 ± 0.01 | 7.17 ± 0.02 | 63 ± 2.6 | 80 ± 10.5 |
| 30 | 7.33 ± 0.01 | 7.17 ± 0.02 | 62 ± 6.6 | 77 ± 4.7 |
| 60 | 7.34 ± 0.02 | 7.18 ± 0.01 | 64 ± 2.4 | 79 ± 2.1 |

**[a] All values are the mean ± the standard deviation (n = 4 except for hyperventilation of 15 minutes (n = 3) and hyperventilation of 30 minutes and 60 minutes (n = 2 each).**

**[b] CSF, cerebrospinal fluid.**

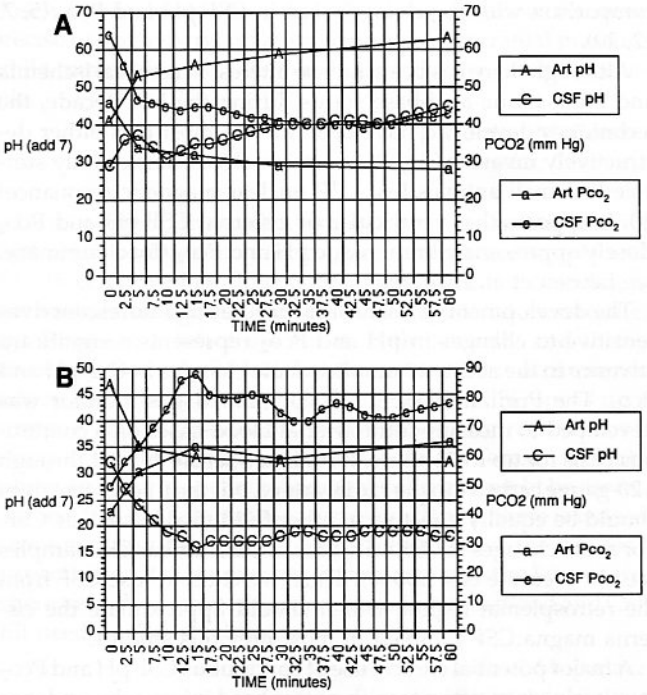


**FIGURE 1. *A*, arterial (*Art*) blood and cerebrospinal fluid (*CSF*) pH (*left vertical axis*) and $Pco_2$ (*right vertical axis*) during hyperventilation for one of the four trials. Arterial blood values are at 0, 5, 15, 30, and 60 minutes; CSF values (using the PB3300) are at every 2.5 minutes from 0 to 60 minutes. *B*, data expressed in the same format as *A* during hypoventilation for one of the four trials.**

comparison with the changes seen in CSF pH and $P_{CO_2}$ (5, 7, 12, 20).

Although there has been intense interest in cerebral ischemia and brain tissue acid-base status during the last decade, the techniques developed have been for the most part either destructively invasive (e.g., tissue microelectrodes) or only suitable for small animals (e.g., $^{31}P$ nuclear magnetic resonance) (9). It appears that ventricular or cisternal CSF pH and $P_{CO_2}$ closely approximate brain tissue pH and $P_{CO_2}$ (for a summary, see Leusen et al. (12)).

The development of a sensor incorporating fluorescent dyes sensitive to changes in pH and $P_{CO_2}$ represents a significant advance in the ability to monitor acute changes in CSF pH and $P_{CO_2}$. The Puritan-Bennett 3300 pH/blood gas monitor was developed to measure intra-arterial blood gases on a continuous basis for up to 72 hours. It utilizes a sensor placed through a 20-gauge catheter in the radial artery, but the fluorescent dyes should be equally effective in other fluid media, such as CSF. For acute changes in CSF acid-base status, lumbar CSF samples are not accurate (see above). Thus, we chose to use CSF from the retrosplenial region, which should approximate the cisterna magna CSF sampled in most previous studies.

A major potential clinical use of continuous CSF pH and $P_{CO_2}$ monitoring is in patients with severe head injury who undergo prolonged hyperventilation for increased intracranial pressure (ICP). It was recognized more than 20 years ago that hyperventilation for long periods (more than 24 hours) might actually be detrimental for controlling ICP, in contrast to its clear benefit for short periods. Raichle and Plum (18) found that the decrease in CBF with hyperventilation was gradually lost over 6 hours, and that with termination of hyperventilation there was an increase in CBF above baseline, which would likely be detrimental for ICP. In unanesthetized goats, Albrecht et al. (1) demonstrated that both CBF and CSF pH had returned to baseline within 6 hours of hyperventilation, and, like Raichle and Plum (18), that CBF exceeded baseline values on termination of hyperventilation. Similarly, Muizelaar et al. (15) showed in the rabbit that pial arteriolar vasoconstriction to hyperventilation was gradually lost over 24 hours, with vessel diameter eventually exceeding baseline. Finally, Muizelaar et al. (14) have demonstrated in comatose patients with head injuries that prolonged hyperventilation for ICP control is probably detrimental in terms of ultimate clinical outcome.

From our findings with the PB3300 monitor using this large animal model, it appears practical to measure CSF pH and $P_{CO_2}$ for at least the 8 hours involved in our studies. It is most likely feasible for the 72-hour limit used for intra-arterial monitoring with the PB3300 monitor. Adaptation of the sensor to fit within an intraventricular catheter would be the next step in using this new technology to monitor CSF pH and $P_{CO_2}$ in humans (e.g., in conjunction with ICP monitoring, as noted in the previous paragraph). From a laboratory research standpoint, continuous monitoring of arterial blood and CSF pH and $P_{CO_2}$ (especially in conjunction with CBF monitoring) may be helpful in studying not only the effects of ventilatory changes, but also cerebral ischemia and the relation between CBF, pH, and $P_{CO_2}$ in arterial blood and CSF.

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## COMMENTS

A sensor incorporating fluorescent dyes sensitive to changes in pH and $P_{CO_2}$ has been developed to monitor arterial blood gases continuously. Using the same technology, the authors have measured acute changes in pH and $P_{CO_2}$ in cerebrospinal fluid (CSF) and found excellent correlation with changes in arterial blood pH and $P_{CO_2}$ in response to hyper- or hypoventilation in an animal model. Being able to place such a monitor within a ventriculostomy catheter may prove useful in a clinical setting wherein determination of CSF acid-base status will reflect cerebral ischemia, as ventricular CSF pH and $P_{CO_2}$ will closely approximate parenchymal values and allow the more precise use of hyperventilation to reduce intracranial pressure while minimizing the likelihood of producing cerebral ischemia.

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In this article, the authors show that the Puritan-Bennett 3300 pH/blood gas monitor can accurately measure pH and $P_{CO_2}$ in cerebrospinal fluid (CSF). First, I did not even know that such an instrument existed for intra-arterial monitoring, and I can see a lot of use for it, both clinically and in the laboratory. Second, the fact that the instrument is accurate not only in blood but also in other fluids such as CSF opens up a further world of possibilities. Nevertheless, for *routine* monitoring of CSF in clinical situations, I do not foresee a bright future, although in a clinical research setting it might be useful. The article is not completely clear as to whether there is indeed a continuous output from the instrument, but if there is (as I suspect), then it certainly will find its way into the laboratory, where very close temporal correlations between blood and CSF still need further elucidation.

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