Cerebral Venous Blood Gas Tensions in Elevated Intracranial Pressure

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SUMMARY Cerebral venous blood gas tensions were correlated with elevated intracranial pressure in spontaneously breathing dogs lightly anesthetized with nitrous oxide/halothane. Intracranial pressure was elevated by infusion of artificial cerebrospinal fluid into a lateral ventricle. Respiration and blood pressure were monitored. The results of these experiments indicate that cerebral venous carbon dioxide tension is increased in association with elevation in intracranial pressure. Moreover, it appears that cerebral venous pCO₂ is effectively regulated at a mean of about 52 mm Hg over a wide range of intracranial pressure.

THE METABOLISM of the brain is remarkably constant under most physiological circumstances. The metabolic state of the brain is reflected by the chemistry of the venous blood, particularly blood gas composition. Assuming that the metabolic rate remains constant, therefore, changes in venous blood gas composition should reflect changes in perfusion.

Although the effect of increasing intracranial pressure (ICP) on cerebral blood flow has been widely investigated, only a few studies have considered the effect of elevated ICP on blood gas tensions. Of those studies, the arterial blood gases were considered but cerebral venous samples were not measured. Johnston et al measured jugular venous pO₂ in the baboon but did not comment further on the blood gas tensions. Arterial blood gas alterations accompanying increased ICP may be an indication of secondary respiratory depression. The effect of increased ICP on cerebral blood gas tensions has not been extensively studied in spite of its potential clinical relevance.

If increased ICP results in increased overall cerebrovascular resistance, the net effect would be a decreased pO₂ and increased pCO₂ of the cerebral venous blood. This study systematically correlates cerebral venous blood gas tensions with elevated intracranial pressure.

Methods

All animals used in these studies were mongrel dogs (18–30 Kg) of either sex. Pentothal sodium (Thiopental), a short-acting barbiturate, was used for induction (20–30 mg/Kg to effect) of anesthesia. Cuffed endotracheal tubes were inserted and connected to a gas anesthesia apparatus. Nitrous oxide 70–80% and oxygen 20–30% were administered at high flow rates to insure that the concentration remained constant. Flow rates were regulated to 300–500 ml/min for oxygen and 1100–1200 ml/min for nitrous oxide. Occasional halothane supplements were given as necessary. Following any halothane supplements, the investigators waited until intracranial pressure, blood pressure and blood gases returned to steady state (approximately 10–15 minutes) before doing any further experimentation. Anesthesia was of suitable depth, duration and extent that animals did not experience pain.

Cannulas were inserted into the aorta via the femoral artery. Blood pressure was monitored by a polygraph. Mean arterial pressure (MAP) was calculated from this measurement. Femoral venous cannulas were inserted for intravenous drug or fluid infusion.

A scalp incision was made using an electrosurgical unit, and the temporalis muscle was carefully reflected from the skull unilaterally. The muscle and the scalp were infiltrated with xylocaine. A cannula (Potts-Courand 18 ga. thin-walled needle) was inserted into the lateral ventricle through a twist-drill hole in the cranium and cemented in place with dental acrylic. Several small lateral holes were made at the end of the cannula to insure patency. Stereotaxic coordinates used were adapted for mongrel dogs from the Lim, Liu and Moffitt atlas. The anterior-posterior reference point was the external auditory meatus. The cannula was inserted at a point 1 cm. anterior the reference point, 1 cm. lateral to the midline and 1–1.5 cm. deep. The cannula was then connected to a transducer for ICP recording. A reservoir containing artificial cerebrospinal fluid was connected to the cannula providing a means of increasing ICP.

For measurements of blood gas tension, arterial samples were taken from the aortic cannula. Cerebral venous samples were obtained from a cannula (15 g. blunted needle inserted into the superior sagittal sinus via a twist-drill hole in the external sagittal crest. The cannula was placed proximal to the junction of the lateral sinuses. Samples were collected in heparinized syringes and blood pH, PO₂, and pCO₂, were determined using a Corning 165 blood gas analyzer. This site was chosen based on the venous outflow method of measuring cerebral blood flow. Rapela and coworkers demonstrated that blocking the lateral sinuses virtually eliminated extracranial contamination of intracranial flow. Acute elevations of ICP completely diminished sagittal sinus outflow, thereby indicating that even under extreme conditions of elevated ICP, there was no extracranial mixing.

Respiration was monitored with a pneumotachometer attached in series with the anesthesia apparatus and connected to a volumetric pressure transducer and polygraph. Animals were breathing spontaneously throughout the experiments. Data were analyzed util-

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Results

Baseline Levels

Baseline arterial and cerebral venous $pCO_2$ values from 55 dogs prior to any increase in intracranial pressure was summarized in Table 1. Arterial blood gas tensions were within normal range. Normal values for dogs are $PaO_2$ 77–102 mm Hg and $PaCO_2$ 31–43 mm Hg. Baseline values in these experiments were $PaO_2$ of 99.6 ± 8.2 mm Hg and $PaCO_2$ of 36.9 ± 5.2 mm Hg.

Inspection of the baseline data in Table 1 indicates a variable relationship between arterial and cerebral venous $pCO_2$. When this data is presented as a scatter plot the following correlation emerges. Figure 1 shows a plot of the arteriovenous $pCO_2$ difference as a function of arterial $pCO_2$. The product-moment correlation coefficient, $r = 0.40$. Despite the wide scatter of values, the correlation is statistically significant at the 1% level of confidence (Null hypothesis: $r = 0$). Thus, as the least squares regression line in Figure 1 indicates, the cerebral arterial-venous difference in $pCO_2$ varies inversely with arterial $pCO_2$.

Over the course of these experiments the overall arterial oxygen tension remained within normal range at a mean of 92.8 ± 9.2 to 97.0 ± 19.6 mm Hg until the cerebral perfusion pressure decreased to about 25 mm Hg or less. Then the mean $PaO_2$ decreased to 67.0 ± 12.5 mm Hg. Arterial $pCO_2$ at this time increased to 47.1 mm Hg ± 3.8 SD. Cerebral perfusion pressure at this lower level is generally considered outside physiological range.

Cerebral Venous $pCO_2$ and Perfusion Pressure

The observed alterations in cerebral venous $pCO_2$ under conditions of increased intracranial pressure may be expressed as a function of ICP per se as well as a function of cerebral perfusion pressure (CPP = MAP − ICP). As the discussion will show, the conclusions and inferences need not be the same.

Figure 2 summarizes the relationship between cerebral venous $pCO_2$ and perfusion pressure. The pooled data of all animals is included, regardless of any other parameters such as respiration or blood pressure. The means shown are the group means for all values within each interval of 10 mm Hg cerebral perfusion pressure. The average number of determinations in an interval is 25. The horizontal lines under the groups represent ranges for which there are no statistically significant differences among means.

The overall analysis of variance, testing the null hypothesis that the variance among groups is equal to the variance within groups, showed a significant ($p <$...
0.001) difference among means for pCO₂. Thus cerebral venous pCO₂ is indeed related to perfusion pressure. Similarly, treating the ranges from 0–59 and 60–129 mm Hg as separate groups revealed a significant (p < 0.001) difference between means. To test for significant differences between pairs of means or sets of means, the Student-Newman-Kuels or LSR (least significant range) tests were employed. The results are diagrammed in figure 2. The horizontal lines represent ranges for which there are no statistically significant differences among means. The diagram illustrates why an analysis of variance revealed that the set7-13 had a significant difference among means. If either group 7 or 13 alone is deleted, the remaining sets are not significantly different. This analysis shows that as perfusion pressure falls to about 60 mm Hg there is relatively sharp inflection in the relationship between pCO₂ and cerebral perfusion pressure. The value at which this inflection occurs corresponds to the lower limit of autoregulation.

The exact level of this inflection cannot be ascertained. It is likely that one of the factors leading to the variance in the venous pCO₂ data is the level of arterial pCO₂. The following experiment is shown as an example of the effect of wide variation in arterial pCO₂. The arterial pCO₂ levels of the overall group did not differ significantly from baseline values until ICP was raised in excess of 40 mm Hg. At this increased ICP value the mean arterial pCO₂ was near the outside limit of normal at 38.6 mm Hg. The contribution of this factor may be assessed by comparing the venous pCO₂ vs CPP plots at different arterial pCO₂ levels altered intentionally in the same animal. Figure 3 shows an example of such an experiment. The dog was paralyzed and artificially ventilated. In the first sequence, the respirator was adjusted to given an arterial pCO₂ of 34.8 mm Hg. In the second, ventilation was decreased and arterial pCO₂ rose to 48.1 mm Hg. Arterial pO₂ was kept within normal limits. The baseline conditions for the two pCO₂ levels are not identical. The hypercapnia was associated with a 25 mm Hg rise in arterial pressure and a concomitant increase in intracranial pressure at 7 mm Hg. Nevertheless, since the critical parameter is cerebral perfusion pressure, the comparison is valid at levels at which the CPP’s can be matched. The results suggest that cerebral venous pCO₂ begins its steepest rise under hypercapnic conditions than in the normocapnic state.

Cerebral Venous pCO₂ and Intracranial Pressure

The venous pCO₂ data (fig. 4) is plotted directly against intracranial pressure. The logarithmic transformation was used in the analysis. As in the previous comparison, the overall analysis of variance showed a significant (p < 0.001) difference among means as compared to the variance within groups. The data, therefore, supports the hypothesis that cerebral venous pCO₂ varies as some function of intracranial pressure. However, as seen in figure 4, more specific tests or multiple comparisons revealed a broad range of ICP values which constitute a nonsignificant set. From this, it appears that cerebral venous pCO₂ is significantly correlated with ICP only at the extreme ends of the range of pressure. Several explanations may be offered for this (see Discussion). Evidence that the blood gas differences at low ICP are significant is supported by a series of experiments in which the blood gas and blood pressure alterations at low levels of ICP were specifically examined. Table 2 is a compilation of data showing the cerebral venous pCO₂ and
pO₂ changes which occurred upon increasing the ICP from 0 to 17 mm Hg. There are 21 measurements from 16 dogs representing a wide range of baseline venous pCO₂ levels. The blood samples at 17 mm Hg ICP were obtained one minute following the increase in pressure. Inspection of this data suggests that a rigorous statistical analysis would be superfluous. However, the experimental design lends itself to analysis by the method of paired comparisons which should be more sensitive than conventional methods since it is not confounded by the differential sensitivities of the animals or differences in sample size. A t-test for paired comparisons (Null Hypothesis: D = 0) for pCO₂ and pO₂ showed that the differences are significant (p < 0.0001). Thus it can be concluded that increasing ICP to levels as low as 17 mm Hg results in significant increases in cerebral venous pCO₂ and decreases in cerebral venous pO₂.

The exact time-course of these changes could not be ascertained. Technical limitations restrict the number of cerebral venous samples to a maximum of about one per minute. Thus, alterations in blood gas composition which occur over this period of time may be missed or attenuated because of dilution or mixing. Figure 5 shows the time profile of cerebral venous pCO₂ following a step increase in ICP to 17 mm Hg in a series of four dogs with intentionally different baseline levels of pCO₂. (Baseline values and standard deviations for the general population are shown in table 1.) To the extent that the sampling problem may or may not have obscured a rapid transient response, there is no evidence that the initial pCO₂ level affects either the latency or magnitude of the response. The time-course of recovery, on the other hand, tends to be shortened at higher levels of pCO₂. The apparent overcompensation seen in the two upper curves of figure 5 was observed relatively frequently and was associated with alterations in respiration and/or mean arterial pressure.

As intracranial pressure was raised stepwise beyond 17 mm Hg the general behavior of venous pCO₂ followed the pattern described in figure 4. In order to shed further light on the source of the variability in the pooled data the relationship between venous pCO₂ and ICP of some representative single animals was examined. Figure 6 shows four such plots. Intracranial pressure was raised in steps of 10 mm Hg at three-minute intervals. The venous blood samples were obtained at
approximately one-minute intervals. The data show the initial rise in pCO₂, the typical plateau region and the second steep rise at the higher levels of ICP. Although the pCO₂ appears to be a relatively smooth monotonic function of ICP, there is a considerable dispersion in slope, particularly at the higher levels. Undoubtedly, this dispersion as well as the variation in initial values for pCO₂ account for the increasing variance in the pooled data (fig. 4).

Discussion
The results of these experiments indicate that there is a definite increase in cerebral venous carbon dioxide tension associated with a rise in intracranial pressure. The most convincing evidence for this conclusion comes from the data shown in table 2. However, the most striking aspect of the relation between cerebral venous pCO₂ and ICP is the constancy of pCO₂ at intermediate levels of ICP (fig. 4). From these results the notion that the cerebrovascular system maintains a remarkably stable venous pCO₂ is self-evident. The plateau region is an indication that venous pCO₂ is effectively regulated at a mean of about 52 mm Hg over a wide range of intracranial pressure. The fact that the regulatory mechanism breaks down at high pressures was already suggested by the PvCO₂ vs CPP data in figure 2. However, it appears that the statistically significant differences in means at the low end of the ICP range also signals a failure of regulation.

The correlation between ICP and blood gas tensions is statistically significant only at the extremes of ICP. This behavior at the lower end of the ICP range was not expected. The mean resting level of cerebral venous pCO₂ in these experiments was 45.6 ± 4.3 mm Hg. However, once intracranial pressure is increased the regulation occurs at a substantially higher (about 52 mm Hg) level of pCO₂. There are at least two possible explanations for this phenomenon. First, increasing the intracranial pressure imposes a fixed resistance to blood flow. Since this resistance reflects the mechanical compression of cerebral veins, it cannot be compensated by vasodilation of this segment of the circulation. In order to overcome the added resistance, a compensatory dilation must occur upstream in the arteries or arterioles, thus shifting the pressure head in a downstream direction. It may be that the differences in venous pCO₂ between zero and e.g., 20 mm Hg ICP represents the necessary stimulus to maintain the upstream vessels somewhat dilated. Although this explanation cannot be entirely excluded, some theoretical problems are encountered. If the upstream resistance decreases, flow should be restored and the venous pCO₂ should again decrease. If the results are indicative of the operation of a regulatory mechanism then the question arises, why is the pCO₂ not regulated at the baseline level of 45.6 mm Hg? This question assumes that, in fact, the cerebral carbon dioxide tension, as reflected by the venous pCO₂, is the parameter which is regulated. This working hypothesis is based on two pieces of indirect evidence. First, alteration in arterial pCO₂ is the only agency known to affect cerebral blood flow under physiological conditions and second, within the limits of measurement error cerebral blood flow remains constant as ICP is increased to levels where cerebral perfusion pressure is decreased to 40–60 mm Hg. The finding of the present study that cerebral venous pCO₂ remains constant over a wide range of perfusion pressure would provide further evidence that CO₂ tension is the controlled parameter if an adequate explanation could be found for the difference between the baseline and the plateau levels of pCO₂ (fig. 2). A probable explanation for this difference may be stated in the following manner.

It is now widely accepted that cerebral blood flow under a variety of conditions, including disease states, is very closely matched to cerebral metabolic rate. It is also known that increased intracranial pressure does not in itself alter cerebral metabolic rate. The present finding that cerebral venous pCO₂ under conditions of normal ICP is significantly lower than the mean venous pCO₂ over a wide range of increased ICP suggests that, under the conditions of these experiments, during the resting state there was a dissociation between cerebral metabolism and blood flow. In other words, the brain may have been "over-perfused" relative to its metabolic requirements. The only known physiological condition where such a dissociation occurs is sleep. The experiments of Mangold and colleagues showed a moderate (10%) but statistically significant increase in CBF during sleep. Since this occurred in the face of a fall in blood pressure, it represents a genuine relaxation of cerebrovascular tone. This effect, frequently cited in textbooks, has never been explained. The vascular relaxation cannot be attributed to changes in arterial oxygen or carbon dioxide tension since these remained relatively constant between control and sleep states. Neither is it due to a change in cerebral metabolic rate which was measured and shown to be unaffected. That sleep is quite different from anesthesia was clearly demonstrated by Mangold et al. Whereas barbiturate anesthesia is associated with a profound decrease in cerebral metabolic rate, nitrous oxide anesthesia is not. To some extent, at least, the animals in the present series of experiments may be regarded as sleeping rather than deeply anesthetized. It seems reasonable to conclude that the mean of 52 mm Hg pCO₂ in the plateau region represents the true set-point for control of this parameter and that the lower resting values of 45.6 mm Hg reflects a supranormal perfusion of the brain.

<table>
<thead>
<tr>
<th>PV CO₂</th>
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<tr>
<td>0</td>
<td>17</td>
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<tr>
<td>Diff.</td>
<td>0</td>
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<tr>
<td>Mean</td>
<td>44.4</td>
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<td>SD</td>
<td>±7.4</td>
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The differences between means at 0 and 17 mm Hg ICP are statistically significant (p < 0.001; t-test). Arterial PO₂ and pCO₂ remained at normal baseline values in these animals when ICP was raised from 0 to 17 mm Hg.
It is evident from figure 4 that as intracranial pressure is increased to the region of 100 mm Hg, cerebral venous pCO₂ is again significantly increased. In keeping with the concept that the intermediate regions of ICP are associated with the operation of regulatory mechanisms, the second increase in pCO₂ probably signifies the failure of these mechanisms and a decreased cerebral blood flow. The steep rise in pCO₂ may be appreciated more by reference to single animal records (fig. 6).

In recent years, most investigators have made use of the concept of cerebral perfusion pressure in relating changes in blood flow to intracranial pressure. This seems reasonable since perfusion pressure is more directly related to flow, taking account of both intracranial and systemic arterial pressures. When the present data are analyzed in terms of perfusion pressure, some new information is gained while other significant relationships are lost. Thus, in examining figure 2, one would not conclude that the level at which pCO₂ appears to be regulated is significantly different from the resting level. This is because the resting level in figure 2 is distributed over a range of values reflecting the broad range of resting blood pressure among the experimental animals. Likewise, it is impossible to say whether the pCO₂ values at CPP levels above 60 mm Hg reflect increased intracranial pressure, since it is known, for example, that at least one dog had a mean arterial pressure of 65 mm Hg before ICP was raised. In other words, compared to figure 4, the plot lacks a meaningful reference point. On the other hand, inspection of figure 4 does not readily evoke the suspicion that there are two significantly different sets of groups above and below about 60 mm Hg perfusion pressure. Interestingly, this break-point corresponds to the generally accepted lower limit of cerebral autoregulation and this point strengthens the conclusion dictated by the result of the statistical analysis.

Previous experiments of other workers have shown that the lower limit of autoregulation during acute systemic hypotension is significantly higher expressed as CPP, than that observed with acute intracranial hypertension. This apparent discrepancy between the reserve capacity of the cerebral circulation under these two different circumstances of reduced perfusion pressure remains unexplained. The presence of a non-significant group (means 3–6, fig. 2) below 60 mm Hg CPP may indicate that in these experiments also CBF autoregulation was reaetively intact at a CPP as low as 30 mm Hg. However, cerebral venous pCO₂ is an index of CBF only if cerebral metabolic rate and arterial pCO₂ remain constant. In these experiments a rise in intracranial pressure frequently stimulated respiration so that the relative constancy of venous pCO₂ in the pooled data may, to some extent, be accounted for by decreased arterial carbon dioxide tension.

The enormous volume of literature on cerebral blood flow contains only a few studies in which cerebral venous blood gas tensions have been subjected to close scrutiny. It is of interest to compare the resting pCO₂ levels in these experiments to those of others. The arterial-cerebral venous pCO₂ difference under normal conditions in man is approximately 10 mm Hg. This is comparable to the mean of 8.6 ± 2.2 mm Hg found in the present study using dogs (table 1, fig. 1). No value has been reported for dogs under nitrous oxide anesthesia. Alberti et al found that in pentobarbital anesthetized dogs the pCO₂ of the sagittal sinus blood was about 7 mm Hg above the arterial level and that the difference increased to 12 mm Hg when the dogs were hyperventilated to an arterial pCO₂ of 17.8 mm Hg. Kety and Schmidt appear to be the only others to notice the disproportionate changes between arterial and cerebral venous blood gases. The data in figure 1 is important for three reasons. First, the wide variation in resting pCO₂ levels probably accounts for much of the variance in the ICP data (fig. 4). Second, since arterial pCO₂ has such a profound effect on cerebral blood flow, it is safe to conclude that resting CBF in these experiments differed among animals. Finally, figure 1 shows that changes in arterial pCO₂ are significantly damped in the cerebral venous blood which represents a closer approximation to the state of affairs in the brain itself. The coefficient of variation for the venous pCO₂ is somewhat less than that for arterial blood although the difference is on the borderline of significance (variance ratio test, 0.05 < p < 0.1). These data suggest that cerebral venous pCO₂ may be more closely controlled than the arterial pCO₂.

The results of this study lead to the prediction that in lightly anesthetized animals, as intracranial pressure is increased to approximately 20 mm Hg, there should be a significant decrease in cerebral blood flow which should then remain relatively constant as ICP is raised further. Unfortunately, no CBF measurements under conditions approximating those of the present experiments have been reported. Careful CBF measurements in the lower ranges of intracranial pressure would be extremely useful. Grubb et al report a steady CBF from approximately 30 mm Hg to 70 mm Hg ICP but do not report CBF values for increasing ICP from baseline up to 28–30 mm Hg. Baseline values from a study by Johnston and Rowan show that for ICP levels ranging from 5.6 mm Hg to 11.7 mm Hg the corresponding CBF values decrease from 49 ml/100g/min to 38.9 ml/100g/min. It would be difficult to draw any conclusions from this small sample, however. Sadoshima et al reported a decrease in CBF when the ICP was raised from a control value of 7 mm Hg to 46 mm Hg in artificially ventilated animals. No values are reported for increases to 20 mm Hg ICP. This range of ICP values has been demonstrated to be clinically significant.

These results have considerable bearing on the question of the site of vascular resistance changes in the cerebral circulation. It was shown that as ICP is increased to about 30 mm Hg, the mean cerebral venous pCO₂ rises from about 46 to 52 mm Hg and that at higher intracranial pressures it remains relatively constant until the ICP is raised to around 100 mm Hg. Although CBF measurements were not made in this study, these data suggest that the initial 6 mm Hg rise...
in venous pCO₂ is not associated with an increase in cerebral blood flow. Indeed, the results suggest a decreased CBF. If a comparable increase in pCO₂ had occurred on the arterial side, there would have been a significant increase in CBF.²⁴ The fact that hypocapnia limited to the venous side of the cerebral circulation does not lead to vasodilation suggests that the cerebral resistance vessels which normally alter their caliber in response to changes in arterial pCO₂ are not influenced by alterations in cerebral tissue pCO₂, i.e., these vessels are not the intraparenchymal arterioles. This consideration places the site of the resistance change in response to alterations in arterial, as well as cerebral tissue pCO₂, at the level of the pial arteries and arterioles. These vessels provide a significant proportion of the total cerebrovascular resistance.²⁵ In fact, pial arteries show sensitivity to norepinephrine and nerve stimulation.²⁶ The present study raises the interesting question of how this feedback regulation is effected.

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