

## The Response of Brain Surface Pressure to Hypercapnic Hypoxia and Hyperventilation

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Intracranial pressures (cisternal cerebrospinal fluid and brain surface pressures) were measured in nine anesthetized dogs during and after experimental hypercapnic hypoxia. Both pressures increased significantly after 20 minutes of hypoventilation with the hypoxic mixture ( $P_{aO_2}$   $20 \pm 7.3$  torr;  $P_{aCO_2}$   $87 \pm 7.9$  torr). When the dogs were subsequently hyperventilated with oxygen, the cerebrospinal fluid pressure rapidly declined, but pressure at the brain surface remained twice the control value. This pressure dissociation was even more striking when the dogs were then given an infusion of distilled water intravenously. These findings suggest that swelling of the brain occurs during hypercapnic hypoxia and is not reversed by an hour of hyperventilation. The lack of correlation between cisternal CSF and brain surface pressures suggests that CSF was displaced from the cranium while brain volume expanded. CSF pressure did not, therefore, reflect the actual pressure of the brain. (Key words: Brain surface pressure; Hypercapnic hypoxia; Hyperventilation; Intracranial pressure; CSF pressure.)

DIFFUSE CEREBRAL EDEMA may occur during cardiac arrest and resuscitation. Although the exact mechanism by which edema occurs is unknown,<sup>1-3</sup> laboratory evidence suggests that hypoxia must be associated with hypercapnia to elicit diffuse edema of the brain.<sup>4</sup> Theoretically, any volume changes in the closed cranium should be paralleled by intracranial (brain, cerebrospinal fluid, and cerebral venous) pressure changes. Cerebrospinal fluid pressure, however, has not proved to be a reliable indicator of swelling of the brain.<sup>5</sup> Recently, a method for measuring brain surface pressure through the intact dura was developed.<sup>6</sup> This method was combined with cisternal CSF pressure measurement in the present investigation to determine whether changes in brain pressure induced by hypercapnic hypoxia can be reversed by reoxygenation and hyperventilation, and whether cisternal cerebrospinal fluid pressure reflects brain pressure during and after hypercapnic hypoxia.

### Materials and Methods

Nine healthy mongrel dogs (average weight  $14.5 \pm SD$  1.5 kg) were anesthetized with sodium thiopental (30 mg/kg, iv), and intravenous infusion of 5 per cent dextrose in 0.45 sodium chloride solution was started. The tracheas were intubated with cuffed endotracheal tubes and the lungs were ventilated mechanically with a fixed-volume respirator (Harvard pump), using a mixture of 50 per cent oxygen in air. The left femoral artery and vein were cannulated with polyethylene catheters for continuous pressure recording and blood sampling. Blood was analyzed with direct-reading electrodes for  $pH_a$ ,  $P_{aCO_2}$ , and  $P_{aO_2}$  (Instrumentation Laboratories 113-51). All values were corrected for temperature, measured with an esophageal thermistor. A 19-gauge spinal needle was introduced

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Received from the Departments of Anesthesiology and Mechanical Engineering, University of Florida, Gainesville, Florida 32601, the V.A. Hospital, Gainesville, Florida 32601, and the Surgical Research Laboratory of the Long Island College Hospital, Brooklyn, New York. Accepted for publication July 30, 1971. Supported in part by a Clinical Investigatorship and by a Research Grant RCS-4, sponsored by the Veteran's Administration Hospital, Gainesville, Florida 32601, and by the General Research Support Grant from the National Institute of Health FR-05362-09. A summary of this paper was presented at the Third European Congress of Anesthesiology, Prague, Czechoslovakia, August 31-September 4, 1970. The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

TABLE 1. Effects of Changing Blood-Gas Tensions on Mean Aortic ( $P_a$ ), Central Venous ( $P_{cv}$ ), Cisternal Cerebrospinal Fluid ( $P_{csf}$ ) and Brain Surface ( $P_{brs}$ ) pressures\*

	Normocarbina	Hypercarbia and Hypoxemia	Hypocarbina	Hypotonic Edema†
pH <sub>a</sub>	7.38 ± 0.05	6.95 ± 0.11	7.65 ± 0.06	7.64 ± 0.08
P <sub>aCO<sub>2</sub></sub> (torr)	35.6 ± 1.1	87.7 ± 7.9	15.0 ± 6.8	18.3 ± 6.7
P <sub>aO<sub>2</sub></sub> (torr)	355.6 ± 105.2	20.2 ± 7.3	399.2 ± 114.1	424.8 ± 67.9
Temperature (C)	37.5 ± 1.0	36.6 ± 1.6	35.8 ± 2.1	35.4 ± 2.4
$\dot{V}$ (liters)	3.6 ± 0.6	2 ± 0	13 ± 2.4	10.9 ± 3.0
AwPx (cm H <sub>2</sub> O)	11.5 ± 1.0	1.6 ± 0.7	18.4 ± 4.3	16.5 ± 3.3
P <sub>a</sub> (torr)	120.6 ± 14.1	134 ± 47	121 ± 13.0	120.4 ± 3.4
P <sub>cv</sub> (cm H <sub>2</sub> O)	3.0 ± 1.2	13.7 ± 5.7‡	8.6 ± 4.1‡	7.2 ± 3.9
P <sub>brs</sub> (mm H <sub>2</sub> O)	222.5 ± 74.6	717.9 ± 216.2‡	517.4 ± 285.6§	846.3 ± 119.7‡
P <sub>csf</sub> (mm H <sub>2</sub> O)	118.9 ± 54.9	407.8 ± 172.0‡	71.7 ± 64.3†	217.5 ± 188.2

\* All values are means ± SD for groups of nine dogs each, unless otherwise noted. Measurements were obtained 5 minutes prior to termination of each phase of the experiment.

†  $P < 0.01$  below control.

‡  $P < 0.001$ .

§  $P < 0.05$  (above control).

¶ Studies of eight dogs.

into the cisterna magna and connected by a short plastic catheter to a pressure transducer (P23BB) and recorder (Honeywell). An opening in the left parietal area was then made by trephination. A pressure transducer was fitted into this opening via a teflon press-fit ring and slightly pressed against the brain surface through the intact dura. The transducer was then allowed to equilibrate for approximately 20 minutes before readings were taken. Technical details of monitoring brain surface pressure may be found elsewhere.<sup>6</sup>

Pressures were recorded, and arterial blood-gas tensions and pH were determined during 15–20 minutes of a steady normocapnic state. Hypercapnic hypoxia was then induced by reducing the minute volume and using 95 per cent nitrogen in air and 10 per cent CO<sub>2</sub> in oxygen mixtures as the ventilating gases. Arterial blood gas tensions were measured frequently, and attempts were made to maintain P<sub>aO<sub>2</sub></sub> values near 20 torr and P<sub>aCO<sub>2</sub></sub> values above 50 torr.

After 20 minutes of hypercapnic hypoxia, the dogs were hyperventilated with oxygen. Acidemia was corrected by intravenous administration of sodium bicarbonate (mEq NaHCO<sub>3</sub> = base deficit × body weight in kg × 0.3).

When CSF and brain surface pressures had reached a plateau with hyperventilation, an intravenous infusion of distilled water (50

ml/kg) was given at a rate of 9.89 ml/min by means of a Harvard infusion pump. The brain surface pressure changes observed in this phase of the experiment were then compared with those of a control group hyperventilated with room air but not subjected to hypercapnic hypoxia. The groups were compared for statistical differences using the Wilcoxon two-sample test.<sup>6,7</sup>

## Results

### EFFECT OF HYPERCAPNIC HYPOXIA

With severe hypercapnic hypoxia (P<sub>aO<sub>2</sub></sub> 20 ± 7 torr; P<sub>aCO<sub>2</sub></sub> 87 ± 7 torr), arterial and central venous pressures increased immediately and reached their maximum changes at 5 minutes. Cisternal CSF and brain surface pressures also increased, parallel to the changes in aortic and central venous pressures. All pressures remained elevated throughout the period of hypercapnic hypoxia except aortic pressure, which decreased 40 to 80 torr in four dogs. In two dogs, the decline in aortic pressure progressed to cardiac arrest. Resuscitation by open-chest cardiac massage, defibrillation, and hyperventilation with oxygen was successful in both animals. The results for the entire group were significant increases in central venous pressure ( $P < 0.001$ ), CSF pressure ( $P < 0.001$ ), and brain surface pressure ( $P < 0.001$ ) (table 1).

## EFFECT OF HYPERVENTILATION

When hypercapnic hypoxia was terminated by hyperventilation with oxygen, central venous pressure declined from  $13 \pm 5$  to  $9 \pm 4$  cm H<sub>2</sub>O, still remaining higher than the control value ( $P < 0.001$ ) (table 1). After 15 minutes of hyperventilation, cisternal CSF pressure had declined to normal. Brain surface pressure, however, remained unchanged, decreased only slightly, or continued to rise despite a marked reduction in  $P_{aCO_2}$  and increases in  $P_{aO_2}$  and  $pH_a$  (table 1). An example of the pressure dissociation between CSF and brain surface pressures is shown in figure 1. Even after 60 minutes, the CSF pressure was below the control value ( $P < 0.01$ ) and brain surface pressure was above the control value ( $P < 0.05$ ) (table 1). Accordingly, there was no correlation between CSF and brain surface pressures ( $r = 0.089$ ).

## EFFECT OF INFUSION OF DISTILLED WATER

When distilled water was infused after an hour of hyperventilation, cisternal CSF pres-

sure gradually increased. After 30 minutes, CSF pressure was not significantly greater than the control value even though it was elevated ( $P > 0.10$ ). In contrast, there was a sharp increase in brain surface pressure (fig. 2) to above both control and hypercapnic hypoxic levels ( $P < 0.001$ ) (table 1). We compared the brain surface pressures in these dogs with those in a previous experiment<sup>6</sup> in which the same infusion was not preceded by hypercapnic hypoxia. For the first 10 minutes of the infusion, dogs with prior hypercapnic hypoxia had faster increases in brain surface pressure than the hypocapnic group without hypoxia ( $P < 0.001$ ). As the infusion progressed, this difference became less marked, but still significant ( $P < 0.01$ ) (table 2).

## CHANGES IN CSF AND BRAIN SURFACE PULSE WAVES

Specific changes in CSF and brain surface pulsations were seen during each phase of this experiment. For comparison, a tracing obtained during the normocarbic control state is shown in figure 3. In this dog intracranial

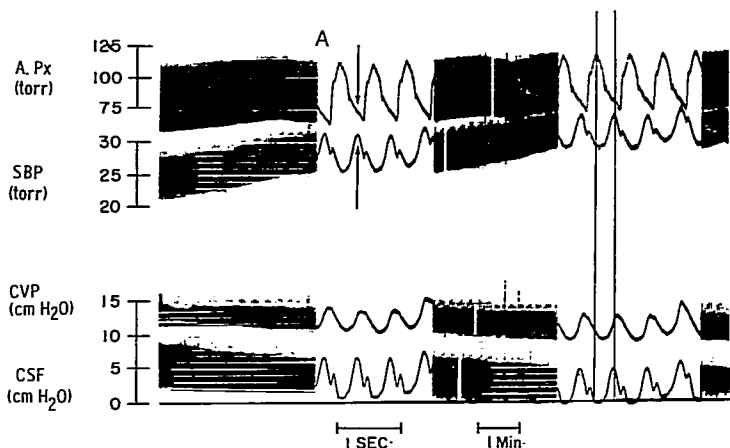


FIG. 1. Effects of passive hyperventilation with 100 per cent oxygen on intracranial pressures in a dog made hypoxic and hypercapnic. Note the pressure dissociation between brain surface pressure (SBP) and cerebrospinal fluid (CSF) pressure after 10 minutes of hyperventilation (A). Also, intracranial pulse-wave contours assume more of the arterial wave characteristic, while venous reflected waves are disappearing. Note at the arrows and vertical time markers that the intracranial pulse waves are a mirror image of the aortic pulse waves (180 degree phase shift).

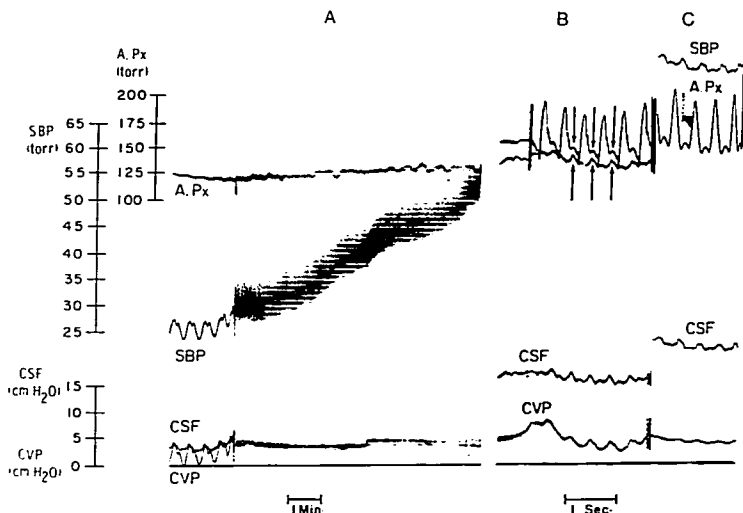


FIG. 2. Composite of typical responses of intracranial pressures (CSF and brain surface) to infusion of distilled water in dogs which have been subjected to hypercapnic hypoxia and then hyperventilated with 100 per cent oxygen. (A), during the first 10 minutes of infusion; note the dissociation of brain surface pressure (SBP) and CSF pressure. After 30 minutes (B), note the persistent phase shift between systolic and brain surface pulse waves. At 60 minutes (C), there is a further increase in SBP out of proportion to the increase in CSF pressure.

pulses (CSF and brain) showed two distinct waves, one almost synchronous with the systemic arterial pulsation and another which presumably was a venous type *a* wave.

With the application of hypercapnic hypoxia, CSF and brain surface pulse waves closely resembled aortic pulsations. As the experiment progressed, however, the amplitude of the intracranial waves (CSF and brain surface) decreased, while the venous type *a* wave became more prominent. This distortion was more pronounced in the presence of severe arterial hypotension and rising central venous pressure (fig. 4). With hyperventilation and restoration of arterial pressure, both CSF and brain surface pulsations resumed aortic-like waveforms, although their peaks shifted 180 degrees with respect to the aortic wave (fig. 1).

With the infusion of distilled water, CSF pulse waves were almost abolished and brain

surface pulsations were moderately damped, while the phase shift observed during hyperventilation remained unchanged (fig. 2). The magnitude of distortion in the pulse contour and the change in amplitude varied somewhat in all nine dogs; however, the phase shift observed following hypercapnic hypoxia, as well as the severe damping of CSF pulsations during infusion of distilled water, remained essentially constant in all instances.

### Discussion

When acute hypercapnic hypoxia was induced, both brain surface and cisternal CSF pressures rose considerably. Since the cranium remained closed, we interpreted the rises in these pressures as a reflection of an increased volume of intracranial content (cerebrospinal fluid, blood, and/or brain water). The rise in CSF pressure is consistent with the findings of Small *et al.*,<sup>8</sup> who believed it

was secondary to increased cerebral venous pressure and intracranial blood volume. In hypoxic and hypercapnic cats, White and co-workers found that both brain and intracranial blood volumes increased, while CSF volume remained unchanged or diminished.<sup>9</sup>

Hypercapnic hypoxia may increase intracranial blood and brain volume by at least three mechanisms. First, acute hypoxia leads to vasomotor paralysis; cerebral blood flow, and presumably cerebral blood volume, in turn become functions of perfusion pressure.<sup>10, 11</sup> Thus, with an increase in arterial pressure, intracranial blood volume increases. As the dilated cerebral arterioles are unable to constrict, the undamped arterial pressure is transmitted to the thin-walled capillaries and veins, resulting in increased cerebral blood volume and elevated cerebral venous and CSF pressures. An increase in cerebral venous pressure may also be induced by increasing cerebral blood flow through the rigid dural sinus,

where the pressure increase impedes outflow from the subarachnoid veins.<sup>12</sup> A further interference with cerebral venous outflow is the simultaneous rise in central venous pressure. In the presence of vasomotor paralysis, expanded cerebrovascular volume, and elevated cerebral venous pressure, the effective cerebral capillary pressure is increased. This force, according to Langfitt *et al.*, leads to extravasation of water and plasma solutes into the brain tissue,<sup>13</sup> causing the brain to become swollen and congested. The third mechanism by which hypercapnic hypoxia may increase intracranial blood and brain volume is the direct action of high  $P_{aCO_2}$ , which increases vascular permeability of the brain (hypercarbic brain edema)<sup>6, 11</sup> and, in conjunction with hypoxia, alters the blood-brain barrier.<sup>4</sup> The high cisternal CSF and brain surface pressures we found reflect this increased intracranial blood volume and swelling of the brain.

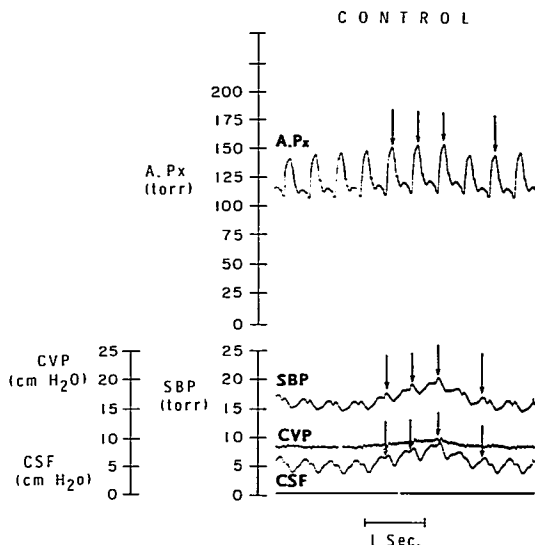
With hyperventilation, brain surface pres-

TABLE 2. Comparison of Brain Surface Pressure Responses to Infusion of Distilled Water in Dogs with Induced Hypercapnic Hypoxia Then Hyperventilated and in Dogs without Prior Hypercapnic Hypoxia

	Brain Surface Pressure (mm H <sub>2</sub> O)				
	0 min	10 min	20 min	40 min	60 min
Dogs with induced hypercapnic hypoxia and hyperventilation					
6S-047	260	420	460	525	590
6S-048	390	520	740	740	740
6S-077	300	410	460	510	535
6S-078	390	550	850	810	770
6S-103	220	270	310	450	520
6S-117	330	510	550	590	590
6S-144	250	400	460	580	650
6S-136	365	500	520	560	585
Mean $\pm$ SD	313 $\pm$ 66	448 $\pm$ 91	544 $\pm$ 173	596 $\pm$ 121	623 $\pm$ 90
P values significant increase more than all controls		$P < 0.001$	$P < 0.05$	$P < 0.01$	$P < 0.01$
Dogs without hypercapnic hypoxia (control group)*					
8F28	140	170	208	310	310
0N65	165	149	158	189	208
0D39	192	228	280	300	305
0D37	160	158	168	184	239
0C94	168	199	243	295	315
0M53	211	215	229	258	275
0S51	223	229	279	309	309
Mean $\pm$ SD	181 $\pm$ 30	193 $\pm$ 34	224 $\pm$ 49	264 $\pm$ 56	280 $\pm$ 42

\* From A. Schettini *et al.*; J. Neurosurg. 34:38-47, 1971.

Fig. 3. Normal tracing obtained in one dog during the control state of normocarbica. The arrows show that peaks of intracranial pulses oscillate almost synchronously with arterial pulses. The second peak visible on intracranial pulsations presumably is a venous type *a* wave.



sure declined somewhat from the peak pressure observed during hypercapnic hypoxia. This initial decrease of brain surface pressure may reflect the reduction in systemic vascular pressures. Following severe anoxia, cerebral arterioles fail to constrict for variable periods of time in spite of reoxygenation.<sup>10</sup> Thus, reduction of systemic vascular pressures (arterial and venous) leads to decreased hydrostatic pressure transmitted to the cerebrovascular compartment, and decreased cerebral blood volume and cerebral venous pressure. With a decrease in cerebral venous pressure, a lower pressure gradient between subarachnoid veins and dural sinus facilitates cerebral venous outflow and CSF reabsorption at the arachnoid granulations.<sup>15, 16</sup> Thus, CSF pressure declines. In the closed cranium, a small volume of fluid displacement is sufficient to produce significant pressure changes.<sup>17</sup>

After an hour of hyperventilation, brain surface pressure was still elevated, even though cisternal CSF pressure was below the control value. This pressure dissociation may be interpreted as an increased cerebrovascular volume and/or a displacement of CSF from the

cranial cavity to accommodate an expanding brain. The volume of intracranial space is virtually constant, irrespective of the pressure generated within it. Under normal conditions, total intracranial volume is maintained relatively fixed by the "interdependence" of the three intracranial fluid compartments (CSF, blood, and brain water). Thus, reduction in one compartment is buffered by fluid redistribution between the other two, and *vice versa*.<sup>18</sup>

In our experiment, increasing cerebrovascular volume alone (posthypoxic hyperemia) could increase cerebral venous and CSF pressures. However, this would not explain the decline of CSF pressure below control levels with hyperventilation. We postulate that, as hyperventilation was instituted, subarachnoid venous pressure decreased. This permitted an increase of CSF reabsorption. More intracranial space was filled by blood and the expanding brain, which further displaced CSF into the spinal subarachnoid space. This expanding brain could have blocked the cisterna magna, and could account for the fall of the CSF pressure to below the control value. It



FIG. 4. Pulsatile and mean pressure tracings from one dog after 15 minutes of hypercapnic hypoxia. Note that at the beginning of the tracing CSF and brain-surface pulse waves resemble aortic pulsations. At the arrows, as circulation fails, intracranial pulsations progressively deteriorate, with loss in amplitude (a), distortion in pulse contour, with prominent venous type *a* waves (b and c), and loss in pulse contour (d), where the arterial and venous pulsatile contributions to the intracranial pulse wave cannot be differentiated.

is also possible that the increased volume of brain abolished the normal communication between ventricles and cisterna magna, resulting in pressure dissociation between supratentorial and infratentorial compartments, with fluid trapped in the ventricles.<sup>17</sup>

These data demonstrate that when intracranial dynamic equilibrium is changed, CSF volume and brain volume change in opposite directions, thus accounting for the poor correlation between cisternal CSF and brain surface pressure changes in our experiments. Schettini *et al.*<sup>6</sup> and Rosomoff<sup>18</sup> have also shown that with hypercarbic cerebral edema or acute swelling of the brain CSF pressure correlates poorly with brain surface pressure.

Failure of the brain surface pressure to return to normal after an hour of hyperventilation suggests either that the cerebral vessels were unresponsive to the decrease in  $\text{PaCO}_2$  or that diffuse edema of the brain occurred. It is possible that, in spite of an alkalotic arterial pH, CSF pH was still acidic as a result of the posthypoxic brain-tissue lacticacidemia and the relatively slow clearance of CSF lactate ions. This might delay the ability of the cerebral vessels to react to reduction in  $\text{PaCO}_2$ .<sup>20, 21</sup> Diffuse edema of the brain also

may have occurred during and after hypercapnic hypoxia, due to both increased capillary hydrostatic inflow and increased capillary permeability. Bakay and Bendixen<sup>4</sup> demonstrated that hypercapnic hypoxia led to extravasation of plasma proteins into the brain and to diffuse cerebral edema. These changes were not seen with either hypercapnia or hypoxia alone. In our study, the responses of CSF and brain surface pressures to infusion of distilled water suggested that increased vascular permeability of the brain was present after induced hypercapnic hypoxia. A similar finding has been demonstrated *in vitro* in the traumatized or hypoxic brain.<sup>22</sup> Thus, it appears that the failure of hyperventilation to reverse the increased brain surface pressure was a result of vasomotor paralysis and/or diffuse edema of the brain.

An important finding of the present investigation was the appearance of specific CSF and brain surface pulse-wave patterns in each phase of our experiment. This should not be surprising, however, since CSF and brain pulse waves are arterial in origin and, thus, their distortion under abnormal hemodynamic conditions can be expected.<sup>23, 24</sup> In hypercapnic hypoxia, the distortion in pulse-wave

contours reflected the fall in arterial pressure and the increases in right atrial and cerebral venous pressures.<sup>23</sup>

With hyperventilation and restoration of systemic blood pressure, this distortion gradually disappeared. A phase shift became the predominant pulse-wave abnormality for the rest of the experiment (approximately two hours), suggesting that cerebral hemodynamics were still abnormal in spite of normal systemic circulation. It has been demonstrated that the phase shift indicates a delay in pulse-wave propagation time,<sup>25</sup> and that transmission of cerebral cortical pulsations can be delayed by increased cerebrovascular distensibility.<sup>26</sup> Therefore, we believe that the phase shift seen in our experiments may be related to the cerebral vasodilatation of the posthypoxic hyperemic phase. This can also explain, at least in part, the failure of hyperventilation to return brain surface pressure to the control value.

When distilled water was infused, the phase shift remained unchanged, suggesting persistent cerebral vasodilatation. The observed damping of waveforms of the arteries of the brain and the obliteration of CSF pulse waves merely reflected the expansion of the mass of the edematous brain.

We conclude that combined severe hypoxia and hypercapnia lead to pronounced increases in both brain surface and cisternal CSF pressures, and to marked distortion of their pulsatile patterns. The increase in brain surface pressure persists after an hour of hyperventilation, even though CSF pressure returns to or below normal. During hyperventilation, the persisting high brain surface pressure is strong evidence of an edematous brain. This pressure dissociation, coupled with the rapid increase in brain surface pressure during infusion of distilled water, indicates an abnormal permeability of cerebral capillaries, which was attributed to posthypoxic hyperemia and diffuse brain edema. The lack of correlation between brain surface and cisternal CSF pressures suggests a reduction of intracranial CSF volume, which allowed more space for brain and/or cerebrovascular expansion. CSF pressure changes clearly do not always reflect changes in brain surface pressure.

The authors acknowledge the invaluable help of Dr. J. I. Thornby for statistical analysis, and Dr. L. Roberts and Miss Pamela Warwick for constructive suggestions in manuscript preparation.

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## Respiration

**LUNG ULTRASTRUCTURE** Morphology which correlates structure and function of the lung requires fixation techniques which preserve the lung in a condition close to its physiologic state. With standard methods, the fixatives are instilled into the airways. The results are adequate for most studies, provided that conditions are standardized with reference to the toxicity of the instillate (it should be isotonic), and the pressure under which it is injected is controlled. This technique, however, does alter the morphology of the extracellular materials, including the alveolar lining layers, surfactant, and the mucous lining of the bronchial tree. To preserve these factors, the author recommends that the fixative be perfused through the lesser circulation, while airway pressure is kept constant, with the transpulmonary and perfusion pressures under close control. A set of five solutions was administered directly into the

pulmonary artery: 1) Ringer's solution containing papaverine sulfate and heparin; 2) 1.5 per cent glutaraldehyde with 1.5 per cent dextran in collidine buffer; 3) Ringer's solution alone; 4) osmium tetroxide with 1.5 per cent dextran in collidine buffer; 5) uranyl acetate in maleate buffer. The dextran adjusts the colloid osmotic pressure to levels similar to blood. With this technique the author was able to visualize clearly the extracellular lining layers and also to identify tubular myelin figures as a major component of the alveolar lining layer. Intravascular perfusion fixation will also preserve other extracellular liquids in the lung, such as the lining layer of airways and intra-alveolar edema. The author suggests that this technique would be of special value in studies of air pollution. (Gil, J.: *Ultrastructure of Lung Fixed under Physiologically Defined Conditions*, *Arch. Intern. Med.* 127: 896-902, 1971.)