The Protective Effect of Hyperbaric Oxygenation in Experimental Cerebral Edema

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Previous communications indicate that hyperbaric oxygenation (HPO) may be beneficial in the management of ischemic disorders of the brain. Other investigators have described the effects of high pressure oxygen on cerebral trauma. The cerebral vasoconstriction caused by hyperbaric oxygenation in combination with the increased available oxygen are factors that might be of value in the treatment of cerebral edema.

This present study was undertaken to evaluate the effect of hyperbaric oxygenation on cerebral edema produced by a slowly expanding intracranial space-occupying lesion.

Method

Cerebral edema was produced by a modification of the technique of Sperl, et al. This method has previously been used to illustrate the effectiveness of steroids in the treatment of cerebral edema.

Forty-four adult mongrel dogs weighing between 15 and 20 kg were used. Operations were performed with sterile technique under intravenous Surital anesthesia. An 8-mm burr hole was made 3 cm anterior to the external occipital protuberance and 2 cm lateral to the midline. Through small dural and cortical incisions a 4 mm diameter ventricular cannula was inserted into the subcortical white matter at a depth of 7 mm. Dry sterilized psyllium seed was gently packed into the white matter with a stylet. The bone button was replaced and the incision closed. Dogs not surviving through the first postoperative day were excluded from the study.

Dogs were divided into two series. The first series consisted of 32 animals in which 1 cc of psyllium seed was inserted into the brain. These animals were used primarily to determine the mortality and morbidity rates. Survivors were sacrificed on the eighth postoperative day.

The second series was composed of 12 animals in which 0.5 cc of psyllium seed was implanted. These dogs were all sacrificed on the third postoperative day at which time an attempt was made to quantitate the degree of cerebral edema. Less psyllium seed was used in this latter group to permit uniform survival to the third postoperative day.

Hyperbaric oxygenation at 3 atmospheres absolute (30 p.s.i.g.) was used in the treatment groups. The animal treatment chamber measured 3 feet in diameter and 8 feet in length. Oxygen-flushing was initially accomplished so that the concentration of oxygen in the chamber was always above 95% at 3 atmospheres absolute. Compression was carried out at 2 to 3 lbs per min. Oxygen flow was sufficient to keep the CO₂ environmental levels normal. Periodic samples of inspired air were tested to assure that O₂ concentration was above 95% and that the CO₂ was not elevated.

Treatment periods under hyperbaric oxygenation were for 45 min. Treatment was instituted 24 hours after the completion of surgery. Hyperbaric therapy was continued at 8-hour intervals unless obvious clinical improvement occurred, in which case treatments were given only twice or once a day. Two animals were exposed to 100% oxygen at ambient pressures for similar durations.

Postoperative hydration was maintained parenterally as necessary. In some animals cisternal punctures were performed after anesthesia with intravenous Surital. Cisternal pressures were measured in representative control dogs and immediately prior to and after therapy in treated animals.

Gross pathological examination of all brains was carried out as close to the time of death or sacrifice as possible. Surviving dogs in the first series were sacrificed on the eighth
postoperative day by intracardiac formaldehyde perfusion. All animals in the second series were sacrificed on the third postoperative day by this method.

The brain was transected and the hemispheres weighed separately. A cross section through the level of the anterior commissure was made, and the distance from the septum pellucidum to the cortical surface on both sides was measured. After formalin fixation, sections of white matter were taken from identical areas of the left frontal region and stained with hematoxylin and eosin for light microscopic examination. The estimated degree of cerebral edema as seen microscopically was graded by a neuropathologist. He was not told whether the specimen came from control or treatment groups.

Results

In the first series, 17 dogs served as controls and 15 were treated by hyperbaric oxygenation. On the first postoperative day animals were only minimally sluggish. Beginning on the second day, control animals showed a progressive downhill course characterized by hemiparesis and decreased level of consciousness. Death occurred in 83% (14 out of 17 animals) by the eighth day (Table 1). This included the two controls given 100% oxygen at ambient pressures. In the hyperbaric oxygen group, progressive neurological deterioration was interrupted. Not infrequently improvement was apparent immediately after treatment. In others, maximum degree of improvement occurred 2 or 3 hours after hyperbaric oxygen exposure. Initially, improvement was temporary in treated animals and regression was seen after 4 or 5 hours. By the fourth or fifth day, however, improvement was maintained in all but the four treatment failures. By the eighth day, surviving treated animals were neurologically normal except for mild contralateral weakness. Mortality rate in this group was 27% (4 out of 15 animals).

Cisternal punctures in control animals showed a steady elevation of pressure on successive days. Cisternal punctures in representative animals performed immediately prior to and after a treatment session demonstrated a consistent drop in pressure (Table 2).

In the first series all brains showed gross evidence of cerebral edema (Fig. 1). There was widening of the sulci and flattening of the gyri, most marked in the untreated dogs. No intracranial hemorrhage was present. Treated brains weighed less on the average. They had a smaller individual difference between hemispheric weights. Cross-sectional hemispheric difference within each brain was greater in the controls. Histological evaluation demonstrated more severe edema in the control group compared to the treatment group. Since treated animals tended to survive longer than the control group, it is difficult to quantitate the difference in the degree of cerebral edema. However, in the second series all animals were sacrificed on the third postoperative day. The results (Tables 3 and 4) paralleled those in the first series.

### TABLE 1

<table>
<thead>
<tr>
<th>Animal</th>
<th>Oxygenation</th>
<th>No.</th>
<th>Deaths</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (17)</td>
<td>Ambient Air</td>
<td>15</td>
<td>12</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Ambient 100% O₂</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Treated (15)</td>
<td>−100% O₂—3 ATA</td>
<td>15</td>
<td>4</td>
<td>27%</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>Dog. No.</th>
<th>Before Therapy</th>
<th>After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>102</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>40</td>
</tr>
</tbody>
</table>

*Pressures were measured immediately before and immediately after treatment with hyperbaric oxygen.
Discussion
These findings suggest that hyperbaric oxygenation has a protective effect against experimentally produced cerebral edema. Mortality and morbidity of animals treated by hyperbaric oxygenation were decreased and cisternal pressures lowered.21,30 Favorable clinical findings were reflected by the pathological material. Treated brains appeared less edematous. The difference between the weights and cross-sectional measurements of separate hemispheres was less in the treated groups. This suggests a reduction in the amount of swelling of the edematous brain afforded by hyperbaric oxygen treatment.30 Light microscopic studies demonstrated less severe edema in treated animals.

Because animals were treated in the awake state and the main intent was to evaluate neurological status and mortality rates, physiological measurements were limited.

However, other experiments in our laboratory have shown consistent arterial pO₂ levels between 1000 to 1500 mm of mercury in dogs treated under similar conditions. Hyperbaric oxygenation, as used in this study, increases the amount of oxygen dissolved in plasma 15 to 20 times.24 The volume of oxygen which can be supplied per unit of blood in terms of arteriovenous extraction ratios is approximately doubled.

It has been demonstrated that hyperbaric oxygenation decreases cerebral blood flow by causing cerebral vasoconstriction.15,16,22,42 It has been debated whether the vasoconstriction is a result of high blood oxygen per se or a secondary change in carbon dioxide.26,41 Even in the presence of cerebral vasoconstriction, the total amount of oxygen available to the brain is believed to be increased,4,16,22,25,30,45 although some authors believe that relief of cerebral anoxia may be negated by the decrease in blood

<table>
<thead>
<tr>
<th>Animal</th>
<th>Minimal or Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (6)</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Treated (6)</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 3**
Degree of edema

**TABLE 4**
Comparison of weights of hemispheres

<table>
<thead>
<tr>
<th>Average</th>
<th>Weight of Hemispheres (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
</tr>
<tr>
<td>Control average</td>
<td>41.5</td>
</tr>
<tr>
<td>Treated average</td>
<td>42.6</td>
</tr>
</tbody>
</table>
flow.\textsuperscript{5,16} Lambertsen, \textit{et al.},\textsuperscript{25} and Jacobson, \textit{et al.},\textsuperscript{15} have shown that blood flow is decreased by approximately 25\%. At 3 atmospheres absolute, additional oxygen dissolved in plasma is increased by 100\% in terms of normal arteriovenous oxygen extractions, thereby increasing available oxygen.\textsuperscript{19,20}

In the present study, the working hypothesis has been that the protective effect of intermittent hyperbaric oxygenation is the result of cerebral vasoconstriction and decreased blood flow in the presence of adequate or increased oxygenation of the brain. Both cerebral anoxia\textsuperscript{20} and increased blood flow\textsuperscript{27,29,31,34,37} are factors that aggravate cerebral edema. Increased blood flow causes further rise in intracranial pressure, additional anoxia, and eventual vasomotor paralysis. Hyperbaric oxygenation serves to break this cycle, presumably by combating the anoxia while at the same time decreasing cerebral blood flow by vasoconstriction.

Dunn and Connolly,\textsuperscript{7} in a series of dogs with experimental head trauma, reported a reduction in mortality rate with treatment by hyperbaric oxygenation or 97\% oxygen at ambient pressure. These authors concluded that additional benefit from hyperbaric oxygen over ambient oxygen was not manifested because of cerebral vasoconstriction. In their study however, animals received only a single 2-hour treatment. Their results, therefore, do not necessarily conflict with the present experiment where animals received multiple intermittent treatments. The duration of treatments and atmospheric pressures used were arbitrarily chosen to avoid oxygen toxicity.\textsuperscript{1,2}

Further experience is necessary before any definitive statement can be made regarding the effectiveness of hyperbaric oxygenation in the management of cerebral edema. Current methods of treating cerebral edema are not entirely satisfactory.\textsuperscript{9,33} It has recently been stated that "the therapy of brain swelling secondary to cerebral vascular dilatation should be directed towards reduction of brain blood volume and not water content."\textsuperscript{26,28} Hyperbaric oxygenation in addition to combating anoxia may accomplish this.

Summary

Hyperbaric oxygenation appears to decrease the mortality and morbidity in experimentally produced cerebral edema. Quantitative evaluation of pathological findings suggests less cerebral edema in the treated group. The mechanism involved may be related to the dual effect of hyperbaric oxygenation in increasing available oxygen while decreasing cerebral blood flow by vasoconstriction.

References


34. PILCHER, C. Experimental cerebral trauma. The fluid content of the brain after trauma to the head. Archs Surg., Chicago, 1937, 35:512–527.


