Clinical Application of Hyperbaric Oxygenation in the Treatment of Acute Cerebral Damage

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There have been many reports of the management of cerebral ischemia by hyperbaric oxygenation (OHP), but few evaluations of the effect of OHP on cerebral injury other than several experimental studies in animals. We are reporting the results of OHP treatment in 66 patients suffering from severe acute cerebral damage.

Clinical Material and Methods

Selection of Patients. Most of the patients selected for this study had had head injuries, and all had evidence of severe brain damage (Table 1). In some cases, severe disturbances of consciousness persisted for about 24 hours or longer after the accident; in other cases, surgical procedures revealed severe brain damage.

The remaining patients were suffering from neurological disorders subsequent to the postoperative course of a brain tumor, cerebrovascular disease, or cerebral ischemia. Brain tumor cases were treated with OHP because they showed no signs of returning to consciousness after surgery. Cerebrovascular cases were treated with OHP because of severe carotid thrombosis, and cerebral ischemia cases because of accidental transient cardiac arrests. All of these patients had serious neurological disorders, and most were comatose.

Twenty-six patients had respiratory disorders requiring use of a respirator.

Clinical Management. The patient was treated in a hyperbaric chamber designed to operate at high pressure and large enough to accommodate the attendant staff and essential monitoring and therapeutic equipment. The OHP treatment was usually given at a pressure of 2 atmospheres absolute (ATA) for 1 hour, once or twice a day; six of the treatments, however, were given at 3 ATA for 30 minutes. Pure oxygen was continuously administered to the patient by non-rebreathing face mask or tracheal tube. Compression was carried out at 0.1 to 0.2 kg/cm²/min until the desired pressure was reached, and decompression was carried out according to Meij\'s new decompression schedule.

Physicians always accompanied the patient in the chamber, checked the vital and neurological signs, and collected arterial blood samples for analysis of oxygen and carbon dioxide (PO₂, PCO₂) and pH. Continuous EEG recordings were examined in 34 treatments of 24 patients. The recording was made on an 8-channel instrument, and qualitative analysis was commonly employed. In 13 cases, changes in cerebrospinal fluid pressure were continuously measured through a catheter inserted intraventricularly. Cerebrospinal fluid (CSF) specimens were collected before, during, and after OHP treatment in 13 cases. CSF lactate was determined by the method of Barker and Summerson and pyruvate by the method of Friedemann and Haugen.

Results

Changes in Neurological Symptoms and Signs. During OHP, 33 patients (50%) showed clinical improvement, 21 of them to a remarkable degree (Table 1), which included restoration of mental as well as neurological function. The most impressive responses were increased awareness and responsiveness. Patients who had been mildly confused became themselves soon after the beginning of OHP, moved extremities, spoke, and responded appropriately to instruction. Other patients who had more se-
were neurological deficits and were comatose rapidly became responsive to painful stimuli and simple commands. We noted that the improvements were generally remarkable in the cases in which the neurological deficits were relatively mild, and were hardly noticeable in the patients who were in deep coma.

The improvements occurred with the beginning of OHP and persisted during OHP. However, most of these favorable responses were temporary, and regression occurred immediately after decompression. Thus, in most patients the picture of clinical improvement by OHP reverted almost completely to the pretreatment level soon after the treatment ended.

However, there were three patients who became convalescent with the definite help of OHP treatments. Especially in one patient, who had suffered a severe head injury and had been admitted to the hospital comatose in a very poor condition, permanent neurological improvement occurred dramatically under OHP treatments. At the beginning of the first OHP treatment, he woke up rapidly and became responsive to simple instruction. The improvement persisted after the treatment and, furthermore, apparently increased in stepwise fashion whenever the patient was treated with OHP. The patient was given OHP treatments seven times during 5 days and was discharged 20 days after the admission with only a mild residual neurological deficit.

There were four cases which showed clinical improvement during OHP but which became much worse afterward; one of these patients died soon after the end of the treatment. No cases showed significant clinical deterioration during OHP except when carbon dioxide (CO₂)-mixed gas inhalations were tried. But there was one patient whose convulsive seizures caused by head injury slightly increased during OHP.

**EEG Changes.** Most of the EEG recordings from patients with cerebral damage were regarded as abnormal, with slowing of the background and prominent activity in delta ranges. During OHP, the most common EEG changes were an increase of fast components in the background, a decrease and lowering of delta activity, and an increase or appearance of definite alpha activity (Fig. 1). These changes were regarded as a reduction of abnormalities, that is, positive improvement in EEG. Of 24 patients whose EEG's were studied (Table 2), some degree of improvement was observed in seven and remarkable improvement in nine. However, of the nine patients who were in very poor condition and in deep coma, only three showed EEG improvement with OHP. Noticeably, no EEG response to OHP was obtained in four cases in which pretreatment EEG recordings showed almost no activity.

Qualitative analysis of 18 cases of severe head injury showed a decrease of delta activity in 10, an appearance or increase of alpha activity in 15, and an increase of fast components in alpha ranges in three (Fig. 2). In general, increase of alpha activity accompanied increase of beta activity. On the other hand, changes in the theta ranges were variable, but in most cases where there was an increase of theta activity there was a decrease of delta quantity.

Most of the EEG changes were noted only during OHP, and, like the clinical changes, regression occurred soon after decompression. There were two cases where the EEG deteriorated significantly after OHP. The EEG improvements were com-

<table>
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<tr>
<th>Cause of Damage</th>
<th>No. of Cases</th>
<th>No. of Treatments</th>
<th>Improvement</th>
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<td>97</td>
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<tr>
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<tr>
<td>Total</td>
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Fig. 1. EEG changes caused by hyperbaric oxygen (OHP) treatment in a 24-year-old woman with neurological disorders after transient cardiac arrest.

monly accompanied by clinical neurological improvements.

Influence on Cerebrospinal Fluid Pressure. The CSF pressure in general fell with OHP after the initial shaking caused by the beginning of compression, and reverted rapidly with decompression. At the cessation of OHP the CSF pressure commonly showed a temporary rebound phenomenon and considerably exceeded the pretreatment level. There were two cases in which the CSF pressure showed little response to OHP, and two in which the CSF showed little rebound phenomenon with decompression and maintained a level considerably lower than the pretreatment one.

The decrease of CSF pressure by OHP was generally more obvious in patients

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</table>

TABLE 2

EEG results of hyperbaric oxygen therapy in 24 patients with acute cerebral damage
whose neurological disorders were milder; in a patient whose CSF pressure was very low, there was almost no response to OHP.

**CO₂ Inhalation.** Three patients suffering from acute cerebral damages were tried on inhalations of CO₂-mixed O₂ gas (2% CO₂ + 98% O₂) during OHP (2 ATA). Immediately after the pure O₂ gas was changed for the CO₂-mixed O₂ gas, the CSF pressure which had decreased under OHP rose rapidly to exceedingly high levels and was accompanied by serious deterioration of neurological signs. Rapid breathing, bradycardia, and hypotension following temporary hypertension occurred in these patients. As pure oxygen was restored, the clinical picture reverted in two cases. In one case, however, the neurological signs increased in severity even after restoration of O₂, and the patient died about 6 hours later.

**Changes of Lactate and Pyruvate Levels in CSF.** There was considerable variation in the CSF lactate level during OHP (Fig. 3). However, it can be seen that CSF lactate/pyruvate ratios have a tendency to decrease slightly under the influence of OHP.

**Discussion**

The results of our study suggest that OHP treatment may have a therapeutic effect on acute cerebral damage and improve neurological disorders and EEG findings, but that the degree of improvement is variable. It is quite possible that the differences in the ef-
fectiveness of the treatment resulted from the great variability of physiopathological pictures of acute cerebral damage. With a few notable exceptions the most favorable results were obtained in cases where the cerebral damage was relatively mild and the treatment was applied in the early period after injury. These observations may support the view that the symptoms and signs of brain lesions due to anoxia are favorably affected by OHP, but those due to irreversible neuronal damage or complete blockage of cerebral blood flow cannot be influenced by OHP. The fact that the improvements of the neurological signs and EEG findings by OHP practically disappear after treatment may indicate that there is some limit of the therapeutic effectiveness of the treatment.

Sukoff, et al.,25,26 reported that CSF pressure was reduced after OHP in dogs with experimentally-produced cerebral edema and compression. We have conducted an extensive study in the normal dog and demonstrated that CSF pressure decreased with OHP and increased with decompression.20 Furthermore, it appeared obvious that when OHP was continued for a long time, the CSF pressure which initially had decreased gradually increased; even for a while after OHP was discontinued the pressure increased to a much higher level than the pretreatment level. The variations in CSF pressure responses to OHP were thought to represent differences in the pathophysiological conditions. It can be seen from our observations that when OHP produced a major change in CSF pressure, the neurological deficit was moderate and the improvement by OHP remarkable; on the other hand, when the CSF pressure was extremely high or low and little changed by OHP, there was no improvement. Based on available evidence it seems likely that when CSF pressure shows little response to OHP, the patient has extensive cerebral damage, a seriously disturbed cerebral blood supply, loss of tonus of the cerebral blood vessels, and/or vasomotor paralysis.

It is well known that anoxic brain tissue produces lactate at a higher rate than does normally oxygenated tissue. Capobianco, et al.,7 found an increase in the CSF lactate/pyruvate ratio in patients suffering from severe brain injury and suggested that the increase may be considered a sign of the severity of injury. Our observations demonstrated that there was a slight decrease in the CSF lactate/pyruvate ratio during OHP, but the degree of the change was not as remarkable as expected. It may be that the results relate to the stage when OHP was applied in the post-traumatic course, or to the lactate and pyruvate clearance from the CSF.

The exact mechanism of the effect of OHP on cerebral damage is not clearly understood. It is logical to believe that the great increase of oxygen dissolved in plasma by OHP may produce a favorable effect on anoxic lesions in the brain.15 Sukoff, et al.,25,26 showed that OHP decreased the mortality in animals with experimentally-produced cerebral edema and compression; they suggested that the mechanism involved may relate to the dual effect of OHP in increasing available oxygen while decreasing cerebral blood flow by vasoconstriction, since cerebral anoxia and increased blood flow are factors that aggravate cerebral edema. On the contrary, Jacobson and Lawson14 used OHP in experimental cerebral infarction and showed that no protection was conferred on a series of dogs treated with OHP compared to normobaric controls. Dunn and Connolly,4 in a study of dogs with experimental brain injury, also reported no significant difference in the mortality of the OHP-treated group (97% O2, 3 ATA) compared to the control group treated with normobaric hyperoxic environment (97% O2, 1 ATA). These authors concluded that there was no additional benefit from hyperbaric oxygen over ambient oxygen because the cerebral vasoconstriction possibly prevented the establishment of collateral circulation. With this in view, CO2-mixed gas instead of pure oxygen has frequently been used in the OHP treatment of cerebral injury or cerebrovascular disorders.5,18,21 Thus, there exists a controversy as to whether cerebral vasoconstriction during OHP is beneficial to the OHP treatment of cerebral damage.

It is well established that OHP decreases cerebral blood flow by cerebral vasoconstriction15,12,15,27 and that, even in the presence of cerebral vasoconstriction, the total amount of oxygen available to the brain increases by OHP.5,15,17,22,24 However, the inference that
OHP causes cerebral vasoconstriction is drawn from findings obtained from normal humans or normal animals.

Our observations clearly demonstrate that in patients with cerebral damage the change in CSF pressure by OHP, which had heretofore been regarded mainly as the result of cerebral vasoconstriction, differs considerably from case to case. It is reasonable to presume that there is so much difference in the pathophysiological condition of each clinical case that not only the response of cerebral vasoconstriction to OHP but also the effect of cerebral vasoconstriction on cerebral damage is different in each case. Cerebral vasoconstriction by OHP may be favorable, as Sukoff, et al., suggested, when cerebral vasodilatation has been caused by brain injury and has played an important part in brain swelling. However, it seems likely that cerebral vasoconstriction by OHP may not be helpful invariably when serious cerebral ischemia and decrease of blood flow has occurred. Although the amount of oxygen available to the brain increases under OHP, the cerebral vasoconstriction caused by OHP may not only prevent the establishment of collateral circulation in the lesion, but may also result in the lack of nutrition due to a greater decrease of blood flow and, furthermore, this may disturb the clearance of catabolites in the brain lesion. Evidence to date indicates that more effective OHP treatment is necessary to improve the impaired cerebral circulation by OHP and also to preserve sufficient cerebral blood supply during OHP; in other words, the abnormal vasodilatation caused by injury needs to be returned to normal and at the same time the abnormal vasoconstriction caused by OHP needs to be prevented. However, it is very difficult to attain this objective.

To prevent cerebral vasoconstriction by OHP, inhalation of CO2-mixed gas instead of pure oxygen has been tried by some investigators. However, the results obtained in our series indicate that inhalation of 2% CO2-mixed O2 gas at 2 ATA is dangerous for the treatment of acute cerebral damage, because it often causes excessive cerebral vasodilatation, results in remarkable brain swelling, aggravates cerebral edema, and, furthermore, unfavorably affects combined acidosis. These results have led to the conclusion that in the OHP treatment of acute cerebral damage it is safer to use pure oxygen for the inhalant gas and that, if CO2-mixed gas is used, the mixed proportion should be large enough to prevent abnormal vasoconstriction and small enough to avoid causing excessive vasodilatation. The use of CO2-mixed gas inhalation in OHP treatment of patients with a very low CSF pressure or those in a chronic stage of a post-traumatic course is still under investigation.

The influence of OHP on cerebral edema itself may be more complicated, although Sukoff, et al., suggested the mechanism of its favorable effect. It is quite possible that treatment with OHP accompanied by cerebral vasoconstrictive action has a favorable effect on brain edema caused by or accompanied by abnormal cerebral vasodilatation. However, we have demonstrated that the frequent or long-continued use of OHP may affect the blood-brain barrier and may increase the blood permeability in normal animals to the brain. Final conclusions cannot be drawn, and further study is necessary.

Ingvar and Lassen reported a patient with focal cerebral ischemia who died shortly after the end of OHP treatment although he showed a dramatic response to OHP during treatment. In our series, there were also a few patients who became significantly worse after OHP treatment. It was thought that their deterioration was inevitable, but the possibility exists that the results may relate to the phenomenon of CSF pressure increase after OHP which was observed in this series. Recently, we have obtained evidence that slow decompression prevents the remarkable rebound phenomenon of CSF pressure after OHP.

Summary

We have reported and discussed the following results in 66 patients suffering from severe acute cerebral damage who underwent hyperbaric oxygen therapy:

1. Neurological improvement was observed in half of the cases and reduction of EEG abnormalities noted in one-third of the cases. However, most of the favorable results were observed only during the treatment, and regressions occurred soon after the treatment.
2. Generally, cerebrospinal fluid pressure decreased with the beginning of the treatment, maintained a low level during the treatment, and rebounded at the end of the treatment. Sometimes for a while after the treatment the CSF pressure rose much higher than the pretreatment level. However, there were variations in the response of cerebrospinal fluid pressure to the treatment from case to case.

3. The use of a mixed CO₂ and O₂ gas as inhalant at high pressure may be dangerous in the treatment of acute cerebral damage. We concluded that pure oxygen is safer.

4. A slight decrease in the lactate pyruvate ratio was demonstrated in the cerebrospinal fluid; this suggested that the treatment may contribute to the repair of cerebral damage.

**Acknowledgments**

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**References**


