THE EFFECTS OF HYPERBARIC OXYGEN ON HISTOPATHOLOGICAL CHANGES OF CEREBRAL ISCHEMIA

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SUMMARY

Hyperbaric Oxygen Therapy is an important treatment in cerebral ischemia caused by cerebrovascular diseases.

In this experimental study, ten rabbit brains with cerebral ischemia were treated with Hyperbaric Oxygen under 2 atm. pressure, and the histopathological findings compared with those of a control group.

We demonstrate that Hyperbaric Oxygen Therapy has a considerable effect both in reducing edema and in preventing micronecrosis and macrocyst formation in ischemic brain tissue.

Key Words: Cerebral Ischemia, Hyperbaric Oxygen Therapy

INTRODUCTION

Hyperbaric Oxygen (HBO) can be used as treatment in a variety of neurological disorders (1). There are several reports concerning HBO usage in cerebrovascular disease, head trauma and cerebral edema (2-4). Holbach et al (5) have emphasized its role in the clinical course of traumatic and non-traumatic spinal cord lesions. HBO is also effective in migraine type headaches through its role in regulating blood flow (6). Hyperbaric Oxygen Treatment (HOT) can also be used in patients with senile dementia, multiple sclerosis and myasthenia gravis (7-10).

It is known that the oxygen consumption of the brain is 500-600 ml/min or 25% of the total body O_2 consumption. More than one litre of oxygen circulates through the brain per minute. Obstruction in this circulation from any cause will induce a reduction in neural processes within two minutes and will be followed by tissue damage in the affected area after five minutes. If the reduced supply of blood continues, infarction or necrosis will occur and the ischemic changes may be with or without bleeding (11).

The leading cause of these ischemic changes are vascular in nature. The vascular lumen may be obstructed by an embolus or by thrombus formation on the endothelial surface of the affected vascular wall (12).

Twenty years ago Whalen (13) showed that HBO causes vasoconstriction and decreases cerebral blood flow, and since then the effects of HBO have been intensively investigated. Recent animal experiments have proved that HBO is effective in preventing hypoxic brain edema (14). It is also reported that HBO will decrease cerebral ischemia and may have a preventative effect on epileptic fits (15). Shiokawa (16) showed that HBO decreases cerebral lactate levels and has a therapeutic effect on cerebral ischemia. HBO produces these effects by increasing the amount of oxygen in the plasma, and the increased partial pressure of oxygen exerts a direçt effect on the cardiac sinus chemoreceptors and cerebral blood vessels (15).

Although there are several reports concerning HOT, its action on histopathological changes within the ischemic brain is not discussed in the literature. The aim of this paper therefore, is to determine the effects of HBO on histopathological changes caused by ischemia in an ischemic rabbit brain model.

MATERIALS AND METHODS

A cylinder-shaped HBO room, 70 centimeters long and 40 centimeters in diameter and resistent to 4 atm. pressure was constructed for this experiment. It was connected to an oxygen tube by a three valve system and had a door and two observation windows. The inside pressure could be monitored and adjusted using a manometer connected to the sytem (Fig. 1). 15 rabbits, 40-50 days old were used. The average weight of the animals was 425 grams and their tolerance to HBO had been previously tested in the Animal Diseases Investigation Institute.

All the rabbits were anesthetized using Ketamine, 0,6mg/kg and the cervical portion of the right internal carotid artery was exposed and clipped temporarily for two hours (Fig. 2). Five rabbits in the control group (O Group) were sacrificed ten days later, their brains removed and coronal brain sections fixed in 10% formaldehyde. The other ten rabbits constituted the medical treatment group (T Group) and were treated with HBO under 2 atm. pressure. Twentyfour hours following surgery, HBO was commenced and applied for four sessions of 30,40,40, and 25 minutes with a

two hours break between each application, for a total of 150 minutes per day. This treatment was continued for ten days. At the end of this period the rabbits were sacrificed and their brains were removed. In both control and treatment groups, brain coronal sections were taken in a plane passing from the point where the septum pellucidum reaches the anterior commissure. Following fixation in formol, paraffin blocks were prepared and five micron thick slices were obtained. Each section was stained with hematoxilen eosin stain, with Bodien stain for the neural tissue, and with Van Gieson stain for the vascular walls and connective tissue. Finally, sections were examined under the light microscope in order to detect any cellular and stromal variations.

RESULTS

Microscopic examination of the prepared slices in the control group revealed karyolytic, karyopyknotic and cytolytic changes in the neurons and glial cells. Microcyst and micronecrosis was detected and macrocyst formation was observed in two cases. Periventricular lymphocyte deposits, large bleeding areas, microvacuolisation and porous stroma were seen in one case each. There was no collateral or wide necrosis (Figs. 3 and 4).

In the HBO treated group, microcyst formation and, degenerative neuronal and glial changes were present in each of the cases. Half of the cases in this group had micronecrotic areas, and three had mild edema. One of the cases had porous stromal changes, another had ependymal cell proliferation expanding into the ventricle. Lymphocyte infiltration was observed in one case (Table 1). There was no macrocyst formation, macronecrosis or collaterals. Bleeding areas and gliosis were also absent (Fig. 5).

DISCUSSION

The resistance of blood flow is higher in veins which are smaller than 1,5 mm in diameter, and in the capillaries. As the erythrocytes pass from the capillary lumen one by one in line, their viscosity is less (Fahraeus Lindguist effect), but when erythrocytes accumulate due to microcirculatory defects, the circulation slows and the viscosity of the blood increases enormously. Erythrocyte accumulation on defective vascular endothelium partially obstructs the vascular lumen and the blood flow stops for a few seconds; and of course this leads to ischemia. HBO may protect against ischemia in three ways (8). Firstly, the higher partial pressure of oxygen in plasma can feed the tissue where erythrocyte accumulation has occured. Secondly, oxygen can spread into the extravascular spaces. This property is evident in partially obstructed capillaries with higher oxygen levels than in obstructed capillaries. Therefore, if the infarction area is large and if there is no circulation, HBO will be ineffective. This explains the effectiveness of HBO in the treatment of strokes. The third effect of HBO is that of relieving brain edema. It causes vasoconstriction and reduces extravasation from the dilated capillaries in the hypoxic tissue. HBO also reduces the swelling of the neurons (6). Saltzman et al (17) have stated that if oxygen transport increases, neurological functions will improve and cerebral tissue death can be prevented in hypoxic cases. Oxygen transport can be increased by HBO (18). The therapeutical effects of HOT may be seen even after a few treatments (19). Akimov et al (2) reported good results in a large series with patients suffering from cerebrovascular accidents. Clinical trials with patients who had become worse following aneurysm surgery have shown that HBO has positive effects on the overall outcome (3,20).

Although the clinical effects of HOT are extensively discussed in the literature, its effects on histopathological changes in the brain are still not clear. In our study we have investigated the pathological changes occuring in cerebral ischemic tissue and the effect of HBO on these changes. Degenerative neuronal and glial changes, micronecrotic foci and microcyst formation were present in both HBO and control groups. It is noticeable that the edema was less in the HOT group when it was compared with the control group. Macrocysts, macronecrosis and bleeding areas which were observed in the control group were not detected in cases treated with HBO (1,21). Increased inflammatory cell infiltration was also detected and is a demonstration of the better blood supply in the HBO group.

We conclude that, although microcysts and degenerative neuronal and glial changes occur in both groups, HOT is effective in reducing edema, decreasing the micronecrosis rate, and in preventing macrocyst formation. Histopathologically, HOT reduces significantly the effects of cerebral ischemic conditions.

TABLE I: HISTOPATHOLOGICAL CHANGES DETECTED IN CONTROL AND TREATMENT GROUPS.

	STROMAL CHANGES				CELLULAR CHANGES		
	Porous stroma	Microcyst formation	Macrocyst formation	Edema	Neuroglial degeneration	Gliosis	Inflammation
CONTROL GROUP	1/5	5/5	2/5	5/5	5/5	2/5	1/5
TREATMENT GROUP	1/10	10/10	0/10	3/10	10/10	0/10	3/10

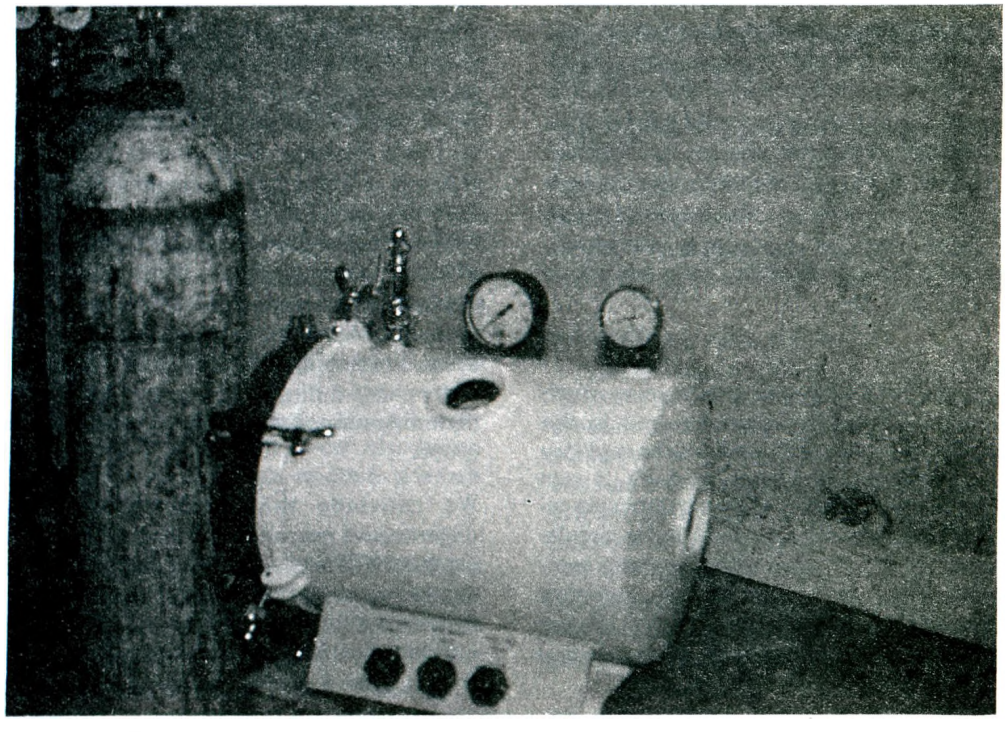

Figure 1: The pressure monitored HBO application room connected to an Oxygen tube.

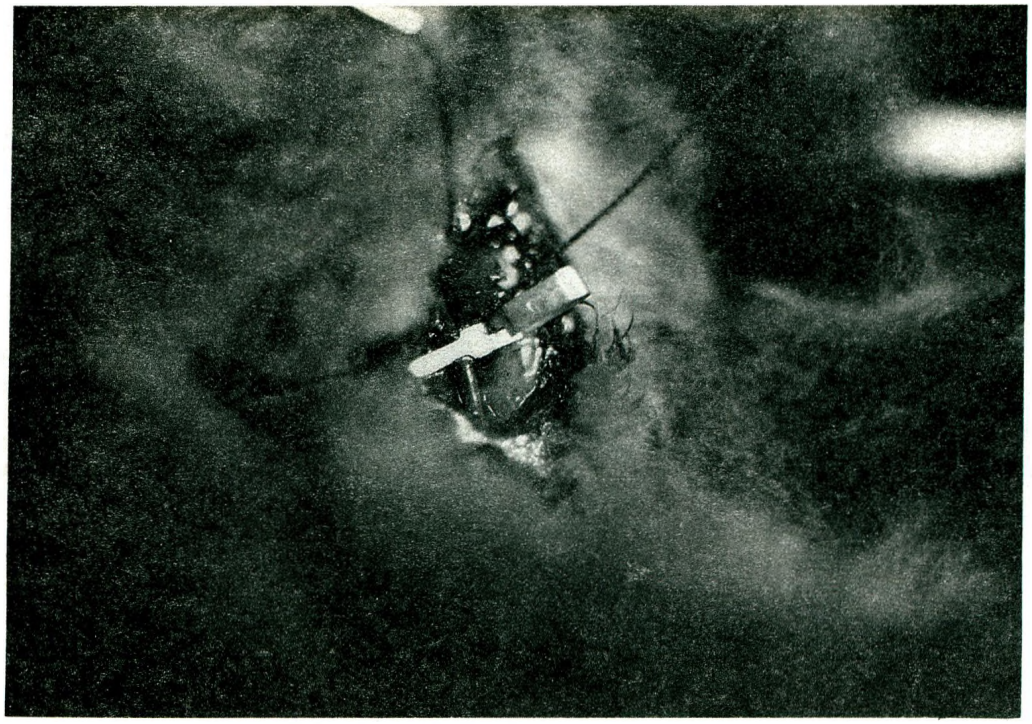

Figure 2: Temporary clip application to the cervical portion of the rabbit internal carotid artery.

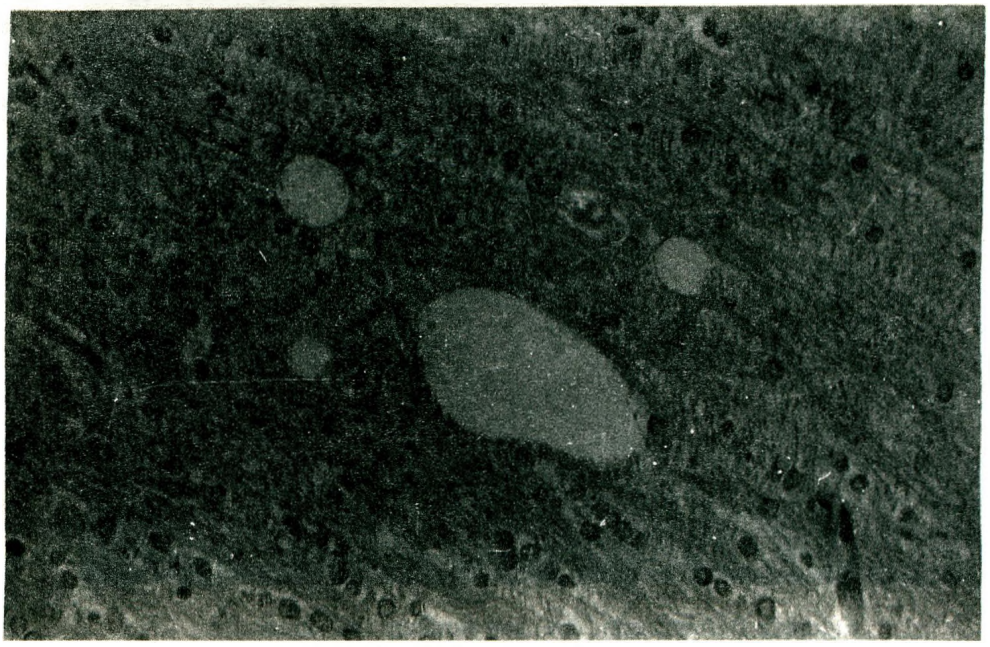

Figure 3: Smooth edged micro and macrocyst formation in rich stroma; O Group. (× 200, HE stain)

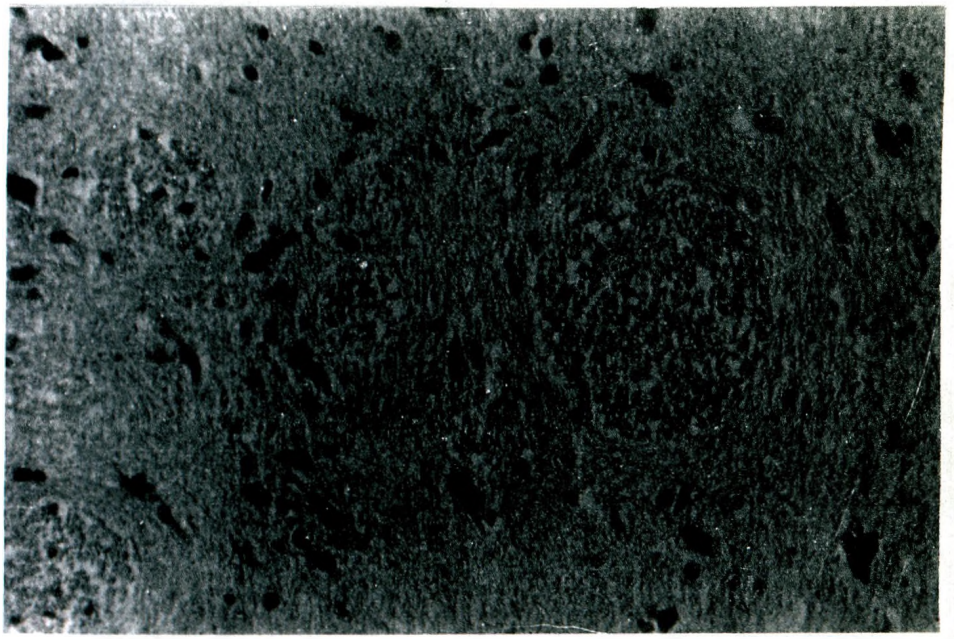

Figure 4: Multiple micronecrotic areas and partially karyolytic ganglion cells; O Group. (x 200 , HE stain)

Figure 5: Demarcation line surrounding the wide necrotic area disappeared after treatment; T Group. (x 100 , HE stain)

REFERENCES

1. *Hayakawa T. Hyperbaric oxygen treatment in neurology and neurosurgery. J Life Sci. 1974;4:1-25*
2. *Akimova GA, Lobzin VS, Sapov IA, Ter-Karapetyan VA. Assesment of the efficiency of hyperbaric oxygenation therapy in early forms of cerebrovascular disorders. Neurosci Behav Physiol 1985; 15:13-17*
3. *Isakov YV, Pravdenkova SV, Shchelkovskii VN. Hyperbaric oxygenation in ruptured cerebral aneurysms during the postoperative period. Zh Vopr Neirokhir 1985; 3:17-21*
4. *Jinnai D, Mogami H, Ioko M et al. Effect of hyperbaric oxygenation on cerebral edema. Neurol Med Chir 1967: 9:260-261.*
5. *Holbach KH, Wassmann H, Hohelucten LK, Linke D, Ziemann B. Clinical course of spinal lesions treated with hyperbaric oxygen. Acta Neurochir 1975; 31:297-298*
6. *Marshall JT. The regulation of cerebral blood flow. Its relation to migraine. Arch Neurobiol (Suppl) 1974; 37:15-25*
7. *Kron RER, Garfinkel SL, Pfeffer SL, Gordon J, Abraham A. Hyperbaric oxygen therapy in senile dementia. In: Abstracts of the 7th International Congress of HBO Medicine, USSR Academy of Sciences, Moscow 1981: 301-302*
8. *Kuhn MAR, Neubauer RA. Observations on urologic data, including cystometrograms on 38 multiple sclerosis patients exposed to hyperbric oxygen at 1,5-2 Atm. Presented in The Gulf Coast Meeting, UMS, March 1-2,1980, Houston, Texas*
9. *Li W. Myasthenia gravis treated by hyperbaric oxygenation. Presented in: The 9th International Congress on Hyperbaric Medicine, March 1-3, 1987, Sydney.*
10. *Massey EW, Shelton DL, Pact V et al. Hyperbaric oxygenation in multiple sclerosis. Neurology 1985: 35:104*
11. *Kapp JP. Uses of hyperbaric oxygen in Neurosurgery. Contemp neurosurgery 1982: 4:1-6*
12. *Marroni A, Data P, Pilloti L. Hyperbaric oxygen therapy at 1,5 or 2 Atm as an adjunct to the rehabilitation of stabilized stroke patients. Presented in: The 9th International Congress on Hyperbaric Medicine, March 1-3, 1987, Sydney*
13. *Whalen R, Heyman A, Saltzman H. The protective effect of hyperbaric oxygenation in cerebral anoxia. Arch Neurol 1966; 14:15-20*
14. *Corkill G, Dhousen K, Hein L, Reitan J. Videodensitometric estimation of the protective effect of hyperbaric oxygen in the ischemic gerbil brain. Surg Neurol 1985; 24:206-210*
15. *Weinstein R, Hameroff SR, Johnson PC, Anderson GG. Effect of hyperbaric oxygen therapy or demethyl sulfoxide in cerebral ischemia in unanesthetized gerbils. Neurosurgery 1986; 18:528-532*
16. *Shiokawa D, Fujishima M, Yanai T et al. Hyperbaric oxygen therapy in experimentally induced acute cerebral ischemia. Undersea Biomed Res 1986; 13:337-344*
17. *Saltzman HA, Anderson B, Whalen RE et al. Hyperbaric oxygen therapy of acute cerebral vascular insufficiency. National Research Council Publications, Washington 1966: 440-446*
18. *Schnakenburg K, Nolte H. Results of electron microscopic studies in the rat brain under oxygen at high pressure. Aerospace Med 1973: 44:259-264*
19. *Sarno JE, Rusk HA, Diller L et al. The effect of hyperbaric oxygen on the mental and verbal ability of stroke patients. Stroke 1972; 3:10-15*
20. *Kitaoka, K, Nakagawa Y, Abe H et al. Hyperbaric oxygen treatment in patients with the postoperative mental signs after direct operation of ruptured anterior communicating aneurysms. Hokaido Igaku Zasshi 1983; 58:154-161*
21. *Isakov YV. Craniocerebral trauma and hyperbaric oxygen therapy. Zh Nevropatol Psikhiatr 1984; 84:762-766*