Identification of Hypometabolic Areas in the Brain Using Brain Imaging and Hyperbaric Oxygen

RICHARD A. NEUBAUER, M.D.,* SHELDON F. GOTTLIEB, PH.D.,t AND AUGUST MIALE, JR., M.D.$

Current neurologic assessments consider idling neurons and ischemic penumbras to be metabolically lethargic and electrically nonfunctional or nonviable. Diagnosis, prognosis, and therapeutics of central nervous system dysfunctions require differentiation between viable and nonviable neurons. It is necessary to develop and document efficacious and safe techniques for reactivating idling neurons. The authors present a case study of a near drowning 12 years earlier. Areas of cortical hypometabolism were identified by using SPECT imaging in conjunction with hyperbaric oxygen therapy (HBOT). Delayed imaging after HBOT (1 hour, 1.5 atm abs) suggested viable but metabolically lethargic neurons. After HBOT (801-hour treatments, monoplace chamber, 1.5 atm abs), marked improvements in cognitive and motor functioning were demonstrated. The data support the hypothesis that idling neurons and ischemic penumbras, when given sufficient oxygen, are capable of reactivation. Thus, changes to tracer distribution after a single exposure to HBOT may be a good prognostic indicator of viable neurons. HBOT may be valuable not only in recovery from anoxic encephalopathy but also from other traumatic and nontraumatic dysfunctions of the central nervous system, including stroke. HBOT in conjunction with physical and rehabilitative therapy may help reactivated idling neurons to remain permanently active.

Cognitive, behavioral, and motor dysfunctions of varying degrees of severity result from trauma and diseases affecting the brain. Delayed improvement of severe neurologic deficits are well-documented in cerebrovascular disorders, in head injuries, after infections of the brain, in multiple sclerosis, after neurosurgery, and after spontaneous arousal from a vegetative coma. The related ideas of idling neurons and the ischemic penumbra (1) have significant implications concerning diagnosis, prognosis, and therapeutics in traumatic and nontraumatic dysfunctions of the central nervous system. Current thought, based on existing techniques of neurologic assessment, consider such tissue to be either metabolically lethargic and electrically nonfunctional, or nonviable. Clinically, it is important to differentiate between viable and nonviable central nervous system neuronal tissue. A technique to differentiate between neuronal tissue that is nonviable and tissue that may be metabolically lethargic and electrically nonfunctional is desirable (1). Such information would be invaluable clinically with particular reference to prognostication, guiding and selecting therapeutic strategies, nursing care, and subsequent design of rehabilitation programs.

SPECT imaging using I-123 IMP as a tracer seems to possess the necessary characteristics with which to identify hypometabolic tissue. IMP is a lipid soluble, indirect agonistic amphetamine derivative that rapidly diffuses across the blood-brain barrier. It is taken up and stored by highly energy-dependent mechanisms of widely distributed cortical and subcortical boutons terminaux of dopaminergic neurons during its first transit through the cerebral circulation (2). When coupled to the fact that perfusion of gray matter is approximately four times greater than that of white matter, such metabolic considerations support the concept that 1-123 IMP SPECT imaging reveals more about phenomena associated with gray than it does white matter. Within 1 hour after injection, an equilibrium is attained between the rates of IMP delivery to and clearance from the brain. After 1 hour, the scan allows visualization of the IMP in the metabolically active boutons (3). IMP has a long cerebral retention time, up to 4 to 5 hours after intravenous injection, that theoretically permits sequential imaging studies on uptake ranging from minutes to hours. Information obtained from imaging done within minutes of the injection presumably reflects energy-dependent bouton uptake of IMP. There is, as yet, no agreement as to the interpretation of the images obtained after a 4- to 5-hour delay (3).

However, electrical function of the brain is closely associated with regional cerebral blood flow, AStrup et al (1) point...
out that the key to neuronal function is not rCBF but oxygen availability. There is a differential sensitivity of various facets of neuronal function dependent upon oxygen availability that has marked implications for neuronal survival. The small but marginal tissue perfusion in the ischemic penumbra implies that these tissues are hypoxic. In hypoxia, the critical Pot is defined as the Pot at which oxygen consumption $(\text{VO}_2)$ becomes less than the normoxic control. Above the critical pot, the $\text{VO}_2$ is independent of $P_{O_2}$. Below the critical $P_{O_2}, \text{VO}_2$ is directly dependent upon the $P_{O_2}$ (4). These concepts are congruent with Astrup et al’s observations. Because of these metabolic relationships and the fact that IMP uptake is metabolism dependent, we view redistribution changes in the scans to represent primarily alterations in metabolism. Also, it is known that changes in function can, secondarily, alter rCBF.

Holbach et al (5) demonstrated that the optimum $P_{O_2}$ for treating head injury is 1.5 atm abs. At this pressure, there is a sufficient increase in the arterial $P_{O_2}$; whatever small blood flow is perfusing the penumbral areas has ample oxygen at a sufficiently high pressure to enhance the rate of oxygen diffusion from the available circulation to the hypoxic tissue to now exceed the critical oxygen values and permit function to be restored to the affected neurons.

The practicality of a technique that appears to distinguish between nonviable and electrically silent neurons was recently reported in the case of a stroke of 14 years’ duration (6). The identification of hypometabolic brain tissue was accomplished by means of hyperbaric oxygen stimulation of the metabolically leathargic and electrically nonfunctional neurons and their subsequent visualization by I-123 IMP SPECT imaging.

We herein present a case in which hyperbaric oxygen (HBO) was used in conjunction with I-123 IMP SPECT imaging to identify hypometabolic areas in the cerebral cortex of a patient with encephalopathy that resulted from an episode of hypoxia 12 years earlier. The long-term diagnostic and therapeutic implications of this observation and its clinical correlation will be discussed.

Materials and Methods

The patient, a 15-year-old girl who had a near drowning accident at the age of 3, was brought to the Ocean Hyperbaric Center by her parents who had heard about hyperbaric oxygen therapy. The imaging and hyperbaric techniques to be employed, which were approved by the Center’s board of advisors, were explained to the parents and their informed consent was obtained. The patient was studied with sequential I-123 IMP SPECT imaging. Between the two studies, which were initially done within 4 hours, a single exposure to HBO was made for 1 hour at 1.5 atm abs in a Vickers monolocal chamber. Before I-123 IMP SPECT imaging, the patient was given several drops of Lugol’s iodine solution to saturate the thyroid binding sites and to prevent a subsequent accumulation of free radioactive iodine. Five to 10 minutes later, the patient was given 4.2 mCi of I-123 IMP intravenously. Her head was carefully positioned so that the entire brain, including the cerebellum, was in the full field of view of the detector, and it was secured to minimize movement. The detector was positioned close to the head so that it would not exceed a 14-cm radius of rotation.

Imaging was performed with the patient’s eyes closed and the lights dimmed. Imaging was begun 15 to 20 minutes after the injection of IMP and was performed by an ADAC ARC 3300 computer interfaced to a Phillips rotating gamma camera. Acquisition was 64 frames at 40 seconds per frame, and the imaging took approximately 45 minutes.

Magnetic resonance imaging was performed on a Diasonics MT/S system operating at 0.35 Tesla before the SPECT study.

Results

The MRI scan showed moderate diffuse central brain atrophy with secondary hydrocephalus. There were no obvious parenchymal lesions.

The baseline initial I-123 IMP SPECT scans (Fig. 1) showed extensive zones of decreased tracer distribution in the right parietal and temporal lobes when compared to the contralateral side, indicating either reduced perfusion or metabolism. The 4-hour delayed scans, after 1-hour exposure to 1.5 atm abs $O_2$ (Fig 1 B), showed that these areas of reduced flow or hypometabolism were filled with the tracer.

Repeat scans were performed after an approximately 2-month hiatus, during which time there were no further HBO treatments. The initial scan (Fig. 2) again revealed a metabolic defect in the right posterior parietal cortex. However, in comparison with the previous scan (Fig. 1 A), there is evidence of mildly improved tracer uptake: The asymmetry previously noted in the temporal lobe is not seen, and the defect in the right posterior parietal cortex is reduced. The repeat 4-hour delayed scan (Fig. 3), during which time the patient was breathing air at 1 atmosphere, revealed minimal redistribution: The improved uptake was not as pronounced as that seen in the preceding study after a single 1-hour exposure to HBO (Fig. 1 B).

Follow-up scans were performed 22 days after the previous study and followed 12 HBO treatments. The patient was first given her 11th HBO treatment. Immediately after the 1-hour HBO treatment, the patient was injected with the tracer and given another 1-hour HBO treatment. Immediately upon exiting the chamber, the patient was scanned, thereby minimizing any reperfusion phenomena. The images represented borderline normal brain I-123 IMP SPECT scans: There were small, subtle areas of hypometabolism in the right posterior parietal cortex.

Four months later, after 61 HBO treatments, the patient had a final I-123 IMP SPECT scan. Imaging was performed immediately after the injection of tracer and repeated after 2 hours of air breathing. The initial views (Fig. 4) indicated that the tracer distribution in the right and left cerebral hemispheres and the cerebellum appeared nearly normal. There was no evidence of a decrease in cerebral blood flow or metabolism. The delayed scans showed no further changes.

Clinical Correlation

Until the time of the near drowning episode, the child’s development was normal. She sat alone at 6 months, walked...
Fig. 1. Axial SPECT brain scan. (A) Before HBOT. (B) After 1-hour HBOT. The colors going from bottom to top on the color bar to the left of the scans represent increasing radioactivity and, by inference, increased metabolism.

Fig. 2. Axial SPECT brain scan (through same region as in Figure 1), 2 months after scan in Figure 1 and before HBOT.

Fig. 3. Axial SPECT brain scan (through same region as in Figure 2), after 1-hour HBOT.

Fig. 4. Axial SPECT brain scan after 61 HBOT treatments and after 2 hours of air breathing.

alone at 9 months, and began to speak at 1 year. There were no problems with feeding or toilet training. When she aroused from the 15-month coma after the accident, she appeared to be mentally retarded. She also required leg braces and was incoordinated. During the 11-year hiatus between coma arousal and HBO therapy, the patient had regular physical therapy but was confined to a wheelchair. Unable to stand, she was often propped up in a box.

As part of the pre- and post-HBO evaluation, the patient was referred to a clinical psychologist. Because of her disabilities, the only tests that could be administered were the Peabody Picture Vocabulary Test and the Vineland Social Maturity Scale. The testing was done in Spanish, her native
language. The exams revealed that she was "... unable to perform any task that involves independent functioning with eye/hand or muscular coordination. She was unable to perform beyond the year seven so her social maturity functioning was very poor... on the vocabulary test... she placed in the 93rd percentile for fourteen year olds... suggesting that her reasoning, her judgment, her discrimination, her understanding of language is probably superior and one would predict that her original intellectual endowment is probably in the high-average to low-supersior range at a minimum. Behaviorally her affect seemed appropriate... she seems to be an alert person with good reality testing. There is no evidence of thought disorder. She seems to have normal intelligence, but her communication of this intelligence is one of her major problems".

After 52 HBO exposures, she was retested using the Peabody Picture Vocabulary Test. Although there was a decrease in percentile standing, the psychologist pointed out that the time factor was halved and the entire test was given in English. He stated that, "She was able to perform much more efficiently in that the rapidity of her functioning resulted in much more intellectual efficiency... I suspect... improvement in synaptic functioning and better associative learning... it would appear that some rather dramatic improvement has occurred." The decrease in percentile standing was not significant because it resulted solely from the change in the testing language, from her native Spanish to English. The fact that she was able to take the test in English is further evidence of recovery of cognitive functioning.

A final evaluation was performed after termination of HBO treatments. He reported "... marked improvement in her clinical symptoms... her speech articulation has improved, and especially her awareness of English... she was more alert... resulting in increased speed of her performance due to her greater span of attention. She worked much faster, was much quicker in problem solving and faster at decision-making judgment. Her speech seemed much improved in that her articulation was clearer. Goal-directed hand movement seemed better coordinated... improved comprehension".

During the years before treatment, the patient stood only in a box. Her mother reported that she is able to stand up for longer periods of time and that she can walk upstairs holding on to the railing with one hand if someone supports her under the other arm. Neurologic consultation confirmed improvement and recommended further hyperbaric oxygen treatment.

**Discussion**

The clinical data support the suggestion that 1-123 IMP SPECT imaging, in conjunction with HBO, has the ability to identify viable neuronal tissue. Analysis of the sequential images indicates that the filling in of hypometabolic cortical areas after a single exposure to 1.5 atm abs HBO suggests the presence of viable but nonfunctioning neurons. It also suggests that the HBO provided sufficient metabolic stimulation to these dormant neurons so that they were able to actively take up the tracer. These interpretations are supported by comparing the increased IMP uptake in the initial and delayed image after one exposure to HBO (Figs. 1A, 1B) with the relative lack of uptake after 4 hours of 1 atm abs air breathing (Fig. 2, 3). If the delayed uptake seen after HBO resulted solely from redistribution phenomena (3), then the same degree of redistribution should have been seen after air breathing. This was not the case. Because the redistribution of tracer was greater after a single exposure to HBO than would have been expected from redistribution alone, we believe that the data support the conclusion that the increased oxygen availability increased the metabolism of viable, though nonfunctioning, idling neurons. We also believe that the combination of HBO and I-123 IMP SPECT imaging is useful for demonstrating the presence of these viable, metabolically lethargic, nonfunctioning neurons.

It is recognized that the interpretation of delayed images is difficult. Such activity may also depict slow flow (impaired diffusion in surrounding edematous tissue), changes in plasma concentrations resulting from enhanced release from storage sites (lungs and bones), uptake by metabolically lethargic cells, accumulation of IMP metabolites by infarcted cells by passive diffusion or pH differentials, and/or a combination of these factors (3). Although redistribution phenomena may explain part of what was observed, we believe that there was a sufficient quantitative difference between the post-HBO (Fig. 113) and post-air scans (Fig. 3) to require an additional explanation - in this case the reactivation of viable, but metabolically lethargic, neurons by HBO.

That these neurons were viable but nonfunctional is also supported by a comparison of the initial scan (Fig. 1B) with the final post-HBO therapy scan (Fig. 4). In the final images, there was essentially no evidence of hypometabolism compared with the baseline scans obtained 8 months earlier. In fact, almost complete absence of hypometabolism was seen by the 12th treatment.

In the 12 years of this patient's therapy, the only change has been the introduction of HBO. Therefore, these comparative physical data imply that long-term HBO therapy reactivate idling lethargic neurons and that this reactivation may be permanent.

It should be noted that a very marked degree of improvement in the scans was evident after only a single exposure to HBO (Figs. 1A, 1B), and that this improvement appeared to have a degree of permanency to it as seen by comparing the first post-HBO therapy scan with the final study (Fig. 4). Whether increased oxygen pressures are capable of reactivating all idling neurons or whether there are classes of hypoxic neurons (only some of which are amenable to reactivation by oxygen) is not known. Astrup et al (1) demonstrated that the critical parameter for tissue functioning is oxygen availabil-
ity rather than blood flow. The increased oxygen tension available under hyperbaric conditions reduces the barriers to diffusion by increasing the driving force for diffusion (7-9).

There are other reports indicating that improved oxygenation may reactivate idling neurons. The restoration of a 7-year unilateral visual field defect in a 58-year-old patient after extracranial-intracranial arterial anastomosis (10) is compatible with the concept. Ingvar and Lassen documented clinical EEG improvement in three or four patients with focal ischemic brain lesions during exposure to HBO (11). A recent study using the gerbil model demonstrated that HBO administered to the animals after stroke increased their survival (12). Saltzman et al. reported that 50% of their patients with acute stroke-induced cerebrovascular lesions demonstrated at least temporary neurologic improvement when exposed to HBO (13). Neubauer (14,15) and Manders (16) have also described the positive effect of HBO on the vegetative state.

The apparent oxygen-induced reactivation of idling neurons suggests that hyperbaric oxygen therapy should be used in conjunction with other forms of physical and rehabilitative therapy in the treatment of traumatic and nontraumatic injury of the central nervous system. Hakim et al. (17) showed that in one-third of their patients who had acute stroke, there was spontaneous reperfusion within 48 hours. They found a loose correlation between the occurrence of reperfusion and clinical improvement and think that patients with spontaneous reperfusion show better levels of recovery (personal communication to RAN and SFG). Moretti, however, used delayed imaging in which there was reperfusion as a good prognostic sign in stroke (18). Our study indicates that there is a correlation between improved cortical function and clinical improvement in the patient, documented by the psychologist’s reports. Although at this time we are unable to correlate a specific improvement in neuronal function with specific improvements in cognitive or motor function in this patient, they appear to be associated.

We conclude that there are groups of metabolically lethargic neurons associated with ischemic brain injury that can be identified by I-123 IMP SPELT imaging in conjunction with hyperbaric oxygen. I-123 IMP SPELT imaging allows for the demarcation of the area affected, and HBO may indicate viability and identify those patients in whom there is potential for improved diagnostic and therapeutic procedures for central nervous system dysfunction (4). There are also implications in forensic medicine pertaining to legal definitions of brain dead.

Acknowledgment

The authors thank R. W. Nichols, RT(N), CNMT, of North Ocean Radiology and Imaging Center for technical assistance.

References