HBO in the Management of Cerebral Palsy

23

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Abstract

Cerebral palsy is a chronic neurological disorder that can be due to several causes of brain damage in utero, in the perinatal period, or postnatally. Hyperbaric oxygen has been shown to be useful in treating children with cerebral palsy. This topic is discussed under the following headings.

Keywords

Birth injury • Brain injury • Cerebral palsy • GMFM • HBO • Hyperbaric oxygen • Oxygen toxicity • Retinopathy of prematurity • Retrolental fibroplasia • Spasticity • SPECT

Introduction: Causes of Cerebral Palsy

The term *cerebral palsy* (CP) covers a group of nonprogressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development. It is the most common physical disability of childhood. Worldwide prevalence is 2.1 per 1000 live births (Oskoui et al. 2013). Problems may occur in utero, perinatal, and postnatal. Infections, traumatic brain injury, near-drowning, and strokes in children suffering from neurological problems come under the heading of cerebral palsy. Diagnosis of cerebral palsy resulting from in utero or early perinatal causes may be made immediately after birth, but more commonly occurs between 15 and 24 months. It is possible that CP may be misdiagnosed for years because specific symptoms may show up very late in childhood. Some of the possible causes of CP are listed in Table 23.1.

Although several antepartum causes have been described for CP, the role of intrapartum asphyxia in neonatal encephalopathy and seizures in term infants is not clear. There is no evidence that brain damage occurs before birth. A study using brain MRI or post-mortem examination was conducted in 351 full-term infants with neonatal encephalopathy, early seizures, or both to distinguish between lesions acquired antenatally and those that developed in the intrapartum and early postpartum period (Cowan et al. 2003). Infants with major congenital malformations or obvious chromosomal disorders were excluded. Brain images showed evidence of an acute insult without established injury or atrophy in 80 % of infants with neonatal encephalopathy and evidence of perinatal asphyxia. Although the results cannot exclude the possibility that antenatal or genetic factors might predispose some infants to perinatal brain injury, the data strongly suggest that events in the immediate perinatal period are most important in neonatal brain injury. These findings are important from management point of view as HBO therapy in the perinatal period (Chap. 21) may be of value in preventing the evolution of cerebral palsy.

Oxygen Therapy in the Neonatal Period

Following World War II, oxygen tents and incubators were introduced, and premature infants were given supplementary oxygen to improve their chances of survival, with levels up to 70 % being given for extended periods. Epidemics of blindness due to retrolental fibroplasia (retinopathy of

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K.K. Jain, *Textbook of Hyperbaric Medicine*, DOI 10.1007/978-3-319-47140-2_23

Table 23.1 Causes of cerebral palsy

Prenatal causes
Amniotic fluid embolus
Anoxia due to cord strangulation
Cerebrovascular accident in utero
Inadequate prenatal care
Maternal abdominal injury during pregnancy
Maternal cardiovascular disorders complicating pregnancy
Maternal drug or alcohol abuse or other toxicity (thalidomide, carbon monoxide)
Maternal infections, i.e., rubella, toxoplasmosis, herpes simplex, syphilis, cytomegalovirus
Maternal metabolic and endocrine disorders, i.e., diabetes, hyperthyroidism
Mitochondrial disruptions
Premature placental separation
Rh sensitization
Underdeveloped (low weight) fetus
Perinatal causes
Cerebrovascular accident at birth
Mechanical respiratory obstruction
Premature delivery, complications of delivery, low birth weight, respiratory distress
Trauma during labor/delivery, hemorrhage, use of forceps, breech delivery
Acquired cerebral palsy as a sequel of:
Anoxic ischemic encephalopathy resultant from near-drowning, near hanging, near-electrocution, cardiac arrest, etc.
Brain tumors
Infections of the nervous system: meningitis, encephalitis, brain abscess
Neurological complications of vaccination
Thrombosis or hemorrhage of the brain
Traumatic brain injury including shaken baby syndrome
Uncontrolled high fever

prematurity—ROP) ensued in the 1950s, which led to a restriction of the level of supplemental oxygen to 40 %. A reduction in the incidence of blindness followed, which appeared to confirm the involvement of oxygen in the development of the retinopathy. The link between the use of recurrent supplemental oxygen and the rise of retinopathy was rapidly accepted, even though it was suggested that retrolental fibroplasia was produced by initially preconditioning a child to an enriched oxygen environment and then suddenly withdrawing the same: the disease occurred only after the child's removal from the high oxygen environment (Szewczyk 1951). It was also noted that a more gradual weaning of the oxygen resulted in a lesser incidence of ROP (Bedrossian et al. 1954). Forrester (1964) found that the best course of action was to return the child to the oxygen environment. Under these circumstances, in many of the patients, the results were encouraging, and vision returned to normal. A slow reduction of oxygen and final return to the atmospheric concentration for several weeks was all that was needed to restore the vision. Thus, there is no rational basis for withholding oxygen therapy in the neonatal period.

The rapid withdrawal of oxygen as the etiology of ROP was reinforced decades later by work implicating the altered regulation of vascular endothelial growth factor (VEGF) in the retina. Pierce et al. (1996) postulated that repeated cycles of hyperoxia and hypoxia in the neonatal period for premature infants may stimulate an increase in VEGF (Saito et al. 1993; Penn et al. 1995). Multiple successful studies on anti-VEGF ocular treatment for ROP (Shah et al. 2016) support this VEGF hypothesis. To prevent ROP, however, Bedrossian's and Forrester's approach has been validated by careful management of oxygen administration and withdrawal that minimizes the cycles of hyperoxia/hypoxia (Chow et al. 2003).

As mentioned in other chapters of this textbook, retrolental fibroplasia is not associated with HBO, either short or prolonged exposures or abrupt cessation of the hyperbaric exposure. Ricci and Calogero (1988) demonstrated that rats continuously exposed to 5 or 10 days of 80 % oxygen developed retinopathy with the 10d rats additionally showing extraretinal neovascularization and total or subtotal retinal detachment. Rats continuously exposed to 1.8 ATA oxygen, however showed no signs of retinopathy and were equivalent to control rats. Using both normal rats and a rat model of cerebral palsy, Calvert showed that doses of HBO as high as 3.0 ATA for 1 h had no structural effect on the retina and showed no evidence of retinal neovascularization (Calvert et al. 2004). In 60 neonates with hypoxic–ischemic

encephalopathy a daily exposure to 1.4, 1.5, or 1.6 ATA HBO improved serum antioxidant levels, neurobehavioral scores, and decreased lipid peroxidation, while causing no retinal damage (Zhou et al. 2008).

It is unfortunate that affected newborns today are deprived of appropriate oxygen therapy because of the fear that it will cause retrolental fibroplasia (see Chap. 32). Some observations indicate that an increased incidence of cerebral palsy has occurred since perinatal high level oxygen administration has been abandoned. Regardless of the controversy about supplemental 1ATA 100 % oxygen usage, there is no evidence that hyperbaric oxygen therapy induces ROP.

Treatment of Cerebral Palsy with HBO

The use of hyperbaric oxygenation in the pediatric patient was relatively common in Russia (see Chap. 56). HBO has been used in Russia for resuscitation in respiratory failure, for cranial birth injuries, and for hemolytic disease of the newborn. HBO was reported to reduce high serum bilirubin levels and prevent development of neurological disorders. In cases of respiratory distress, delayed use of HBO (12–48 h after birth) was considered useless. However, early use (1–3 h after birth) led to recovery in 75 % of cases. This was similar to Hutchison's experience in England with newborn respiratory failure (Hutchison et al. 1963; see Chapter 20, Table 20.2, Human Studies, Hyper Acute Period). Italian physicians began treating the small fetus in utero in 1988 demonstrating a reduction of cerebral damage. Patients were hospitalized before the 35th week and hyperbaric treatments were given every 2 weeks for 40 min at 1.5. The fetal biophysical profile showed a remarkable improvement as soon as the second treatment. Chinese physicians have had extensive experience with HBOT in neonatal resuscitation. A recent review of 20 randomized or quasi-randomized controlled trials for HBO in HIE revealed a near uniformity of results (Liu et al. 2006). While the trials did not use rigorous methodology the reproducible findings were a reduction in mortality and improvement in neurological sequelae, which was consistent with the results of animal studies (Chap. 21).

In the chronic phase, the preponderance of literature suggests a benefit of hyperbaric oxygen therapy in CP. To understand the CP HBOT studies, one must embrace the definition of hyperbaric oxygen therapy stated in Chap. 21 where HBOT is defined as a combination therapy of increased pressure and increased oxygen. As discussed in Chap. 21, both hyperoxia and increased ambient pressure in the hyperbaric chamber are bioactive independently and in combination across the entire phylogenetic spectrum (Harch 2013). In other words, homo sapiens along with all other living organisms is sensitive to changes in both oxygen and ambient pressure. The clinical and clinical experimental difficulty is that no operational method has been devised to separate the effects of pressure from those of hyperoxia. In some of the clinical trials discussed below (e.g., Lacey et al. 2012), the children were exposed to air during the compression and decompression phases of the experiment and then a treatment gas at depth for some period of time. The potential biological effects of oxygen and increased pressure during compression and decompression are mixed with those of pressure, hyperoxia, or both during the time spent during the plateau phase of the treatment. The same is true for the experiments performed in a monoplace chamber with 100 % oxygen; it has been shown that it takes 11 min or more to convert the air in the chamber to greater than 95 % oxygen concentration at 1.5 ATA (Churchill et al. 2013). Therefore, the compression phase is a mixture of increasing pressure and oxygen effects combined with hyperoxic and pressure effects during the plateau phase of treatment and decreasing oxygen and pressure effects during decompression. Importantly, the effects of pressure and hyperoxia begin within 30–60 s of compression (Harch 2013). The sum of these facts converge on the conclusion that all of the purportedly "controlled" CP studies are multi-dosing studies except for the (Packard 2000; Sethi and Mukherjee 2003; Mukherjee et al. 2014) studies where the comparison control group was not subjected to pressurization or hyperoxia.

Awareness of potential for HBOT in CP began at the conference "New Horizons for Hyperbaric Oxygenation" in Orlando, Florida, in 1989. Data were presented on 230 HBO-treated young CP patients from 1985 to 1989 in Sao Paulo, Brazil (Machado 1989). Treatment consisted of twenty 1.5 ATA/1 h HBOTs, once or twice/day (100 % oxygen), in a Vickers monoplace chamber. The results showed significant reduction of spasticity: 50 % reduction in spasticity was reported in 94.78 % of the patients. Twelve patients (5.21 %) remained unchanged. Four patients (1.73 %) experienced "convulsions during the course of treatment, but not in the chamber." Follow-up at 6 months or more included only 82 patients, but 62 of these (75.6 %) had lasting improvement in spasticity and improved motor control. The parents reported positive changes in balance, attention, and "intelligence with reduced frequency of convulsions and episodes of bronchitis." Twenty patients were unchanged. Zerbini (2002) presented results of a continuation of this work at the 2nd International Symposium on Hyperbaric Oxygenation and the Brain Injured Child held in Boca Raton, Florida. Two thousand and thirty patients with chronic childhood encephalopathy were treated from 1976 to 2001. Two hundred and thirty-two children were evaluated with long-term follow-up, age range from 1 to 34 years. Improvements were noted in spasticity (41.8 %), global motor coordination (18 %), attention (40.1 %), memory (10.8 %), comprehension (13.3 %),

reasoning (5.60 %), visual perception (12.9 %), and sphincter control (6.5 %). It was concluded from this study that HBO therapy should be instituted as early as possible in such cases.

At the same conference (Chavdarov 2002), Director of the Specialized Hospital for Residential Treatment of Prolonged Therapy and Rehabilitation of Children with Cerebral Palsy in Sofia, Bulgaria, presented a study on 50 CP children: 30 spastic, 8 ataxic/hypotonic, and 12 mixed. Measurements included nine tests of motor ability, mental ability, functional development, and speech. Overall psychomotor function (single or combined) improved in 60 % of the patients following 20 consecutive days of 1.5–1.7 ATA/40–50 min once daily HBOTs. Motor ability improved in 41 %, mental abilities in 35 %, and speech in 43 % of children with abnormalities of each of these functions. Four experienced "unwanted effects, including seizures, oral automatic movements, hyperesthesia of right face-part, extreme pulse-rate increasing (between 7 and 10 treatments). All unwanted effects disappeared immediately after the stopping of HBO."

The first North American case of CP treated with HBO was in 1992 (Harch et al. 1994). The child was a non-ambulatory 4.5-year-old boy with hypotonic CP secondary to a traumatic precipitous birth. After eighty 1.5 ATA/90 min HBOTs the child acquired gait with fingertip support for balance, improved coordination, increased awareness, and increased alertness. Dr. Richard Neubauer began treating CP in 1995 and a number of cases were treated at freestanding sites in the U.K. by 1998. Based on a small positive case experience in the U.K. a charity to treat CP and brain-injured children, Hyperbaric Oxygen Trust, was established in the late 1990s. Through 2003 the Trust, renamed Advance, had treated over 350 unpublished cases. This positive experience included a few patients from Montreal who were influential in raising money for the first formal pilot trial of HBOT in cerebral palsy (Montgomery et al. 1999).

Published Clinical Trials

Montgomery et al. (1999) involved 23 children (10 female, 15 male; age range 3.1–8.2 years) with spastic diplegia who had an absence of previous surgical or medical therapy for spasticity, and a 12-month clinical physiotherapy plateau. The study was performed at McGill University Hospital's Cleghorn Hyperbaric Laboratory in a monoplace chamber at 1.75 ATA (95 % oxygen) for 60 min daily and at the Rimouski Regional Hospital in a multiplace chamber (1.75 ATA/60 min, twice daily) for 20 treatments in total. The Gross Motor Function Measure (GMFM), fine motor function assessment (Jebsen's Hand Test), spasticity assessment (Modified Ashworth Spasticity Scale), parent questionnaire, and video analysis were performed pre and post HBOT. Results were an average of 5.3 % improvement in GMFM and a notable absence of complications or clinical deterioration in any of the children. "Cognitive changes" were observed, but these were nonspecific. Video analysis was also positive. The obvious flaws of this study were the lack of placebo control and the application of two different HBO protocols. The assessment tools utilized also had inherent variations. Montgomery et al. achieved improvement in CP children using 20 treatments at 1.66 ATA oxygen ((1.75 ATA 95 % O_2)/60 min), but the children experienced rapid regression of neurological gains after cessation of treatment (personal communication from the authors). The number of treatments was inadequate as the authors of this chapter had recommended 40 treatments at 1.5 ATA/60 min; consolidation of gains does not occur until 30–35 treatments. This first study, however, provided useful data regarding the potential efficacy of HBO therapy and provided the justification for a larger controlled, randomized study.

That larger "controlled" trial was performed by the same and additional investigators in 2001 "with intriguing results" (Collet et al. 2001). It was the first multi-dosing study of HBOT in CP and was not a true controlled study. The study included 111 CP children (ages 3–12 years) that were randomized into two groups who received forty 1 h treatments of either 1.75 ATA 100 % oxygen or 1.3 ATA room air (the equivalent of 28 % oxygen at 1 ATA). Half of the children were treated in a monoplace chamber by themselves and half in a multiplace chamber where the parents accompanied the children. Gross and fine-motor function, memory, speech, and language were assessed. Statistically significant improvement in global motor function occurred in both groups (3 % in the hyperbaric air group and 2.9 % in the hyperbaric-oxygen group). Although the results were statistically similar in both groups, the HBO-treated group had a more rapid response rate in the more severely disabled children. Cognitive testing was performed on 75 of the 111 children who could comply with testing (Hardy et al. 2002). Children in both the oxygen and air groups showed better self-control and significant improvements in auditory attention and visual working memory compared with the baseline. However, no statistical difference was found between the two groups. Furthermore, the purported "sham" group improved significantly on eight dimensions of the Conners' Parent Rating Scale, whereas the oxygen group improved only on one dimension. Most of these positive changes persisted for 3 months. No improvements were observed in either group for verbal span, visual attention, or processing speed.

Unfortunately, the Collet study used both a higher dose than what had previously been used 1.75 ATA of 100 % oxygen for 60 min (40 treatments), and a lower dose, 1.3 ATA air for 60 min and 40 treatments, i.e., a 30 % increase in oxygen for the controls. These doses of HBO had not been used pre-

viously in CP patients. The oxygen dose was possibly an overdose (Harch 2002) and likely inhibited the HBO group' gains. Evidence for this was seen in the GMFM data where five of the six scores increased in the HBO group from immediate post HBO testing to the 3-month retest versus 3 of 6 scores in the controls. Possibly, some of the negative effects of 1.75 ATA had worn off in the 3 months before final testing. The serendipitous flaw in the study was the 1.3 ATA air control group which was not a control group, but another dose of hyperbaric therapy. This underscored the fact that the ideal dose of HBO is unknown in chronic pediatric brain injury, but it suggested that oxygen signaling may occur at very low pressures since biological effects of very slight increases in pressure have been documented across the entire phylogenetic spectrum (Macdonald and Fraser 1999). The equivalent Collet air dose of hyperbaric therapy has been demonstrated to be effective in improving SPECT as well as attention and reaction times in toxic brain injury (Heuser et al. 2002). Collet explained the beneficial effect in the air group as a parent participation effect, an explanation that was refuted by the 50 % of children who underwent HBOT in the monoplace chambers without the accompaniment of their parents. The beneficial effect in the Collet air group could only be explained by the beneficial effects of slightly pressurized air rather than the act of participating in the study. This was also the leading explanation of the U.S. Agency for Healthcare Research and Quality in their review of HBOT in stroke, traumatic brain injury, and CP (AHRQ 2003).

The controversy regarding this study is unresolved, but the study has raised some very important issues and questions about the validity of "mild" HBO (1.3–1.35 ATA air or oxygen-enriched air). The first issue is that 1.3 ATA ambient air was not an inert or true placebo, but had a real effect on the partial pressure of blood gases and perhaps other physiological effects as well (Macdonald and Fraser 1999; Harch 2013). Compressed air at 1.3 ATA increases the plasma oxygen tension by 50 % from 12.7 kPa (95 mmHg) to 19.7 kPa (148 mmHg), a notable increase for a reactive substrate. Rather than answer the question of effectiveness of HBO in CP, the Collet study and its offspring (Hardy et al. 2002) substudy confused the hyperbaric and non-hyperbaric scientific communities and prompted a review of longstanding overlooked scientific literature on the effects of "micropressure" (Macdonald and Fraser 1999; Harch 2013). The unequivocal finding of these studies is that both pressure protocols achieved statistically significant objective durable neurocognitive and motor gains, a phenomenon that cannot be attributed to placebo. This reinforced the findings of the other noncontrolled studies in the chronic category (Chap. 21), and was strengthened by the studies using functional brain imaging as surrogate markers (Harch et al. 1994; Neubauer 2002; Golden et al. 2002).

The United States Army Study on Adjunctive HBO Treatment of Children with Cerebral Anoxic Injury

Shortly after the previous studies were begun, physicians at the US Army base in Fort Augusta, Georgia conducted a small study on functional outcomes in children with anoxic brain injury (Waalkes et al. 2002). Eight volunteer (parental) subjects with varying degrees of CP and one near-drowning victim were included in this investigation. Of the CP cases studied, the mean age was 6.4 years (range 1.0–16.5 years), and the near drowning patient was 5.6 years of age seen 1 year post incident. Pretreatment evaluation included the GMFM, the Modified Ashworth Scale (MAS) for spasticity, rigidity, flexion/extension, the Functional Independence Measure for Children (WeeFIM) regarding self-care, sphincter control, transfers, locomotion, communication and social cognition, video, 24-h time measure, parental questionnaire, and single photon emission computerized tomography (SPECT) scanning. Testing was conducted every 20 treatments with the exception of SPECT and parental questionnaire which were completed at 40 and 80 sessions. Importantly, all children continued existing physical and occupational therapy during the study.

The study tested the 80 HBOT protocol underway in the IRB-approved Perfusion/Metabolism Encephalopathies Study of Harch, Gottlieb, and Van Meter in New Orleans (Harch 2010) (1.5 ATA/60 min in blocks of 40 treatments with SPECT and video exams), but at a higher pressure of oxygen (1.7 ATA). All subjects received 80 HBO treatments in a multiplace chamber (100 % oxygen) at 1.70 ATA (60 min for each session) daily (Monday–Friday) for 4 months. Each patient served as his or her own control as compared to the baseline scores. Baseline and serial evaluations showed improvement in gross motor function and total time necessary for custodial care in eight children with CP. Improvements in GMFM in the categories of lying and rolling, crawling and walking, sitting and walking, running and jumping were statistically significant ($p < 0.05$). The total time necessary for parental care was statistically less ($p < 0.03$ %). On the parental questionnaire, overall improvement was indicated through the end of the study. Three children demonstrated improved swallowing function and were able to ingest a variety of liquids and foods; there was reduction in strabismus in two subjects, nystagmus was resolved in one participant, and one patient experienced complete resolution of a grade 3 vesicoureteral reflux, obviating the need for surgery. Unfortunately, the SPECT scan results were omitted due to multiple technical and procedural problems.

Overall improvement was 26.7 % at 30 treatments, up to 58.1 % at 80 treatments. These improvements were nearly an order of magnitude higher than the (Montgomery et al. 1999) study and any subsequent study. Explanations include

non-blinded evaluators, small sample size, combined HBOT and other therapies, and other unexplained factors. Their conclusions were that HBO therapy seemed to effect overall improvement in CP (with little response in the near-drowning case), although the optimum number of treatments remained undetermined, since the improvements were noted at the end of the study. They advised further research and follow-up studies to determine the true potential of HBO for children with anoxic injury and CP.

The New Delhi Study of HBOT in CP

Based on the above experience Drs. Sethi and Mukherjee in New Delhi conducted a randomized prospective controlled trial of HBOT in CP (Sethi and Mukherjee 2003). Thirty subjects were randomly assigned to either standard occupational (OT) and physical therapy (PT) or HBO plus OT/PT. Children also underwent home physical therapy. Children 2–5 years old with all types of CP were included and had a SPECT scan showing presence of recoverable penumbra. HBO patients received 40 HBO treatments at 1.75 ATA/60 min 6 days/week. Gross motor ability was measured using Norton's Basic Motor Evaluation Scale before HBOT and after 6 months of OT/PT or 6 months of OT/PT and HBOT. Both groups improved significantly, but the improvement in the HBO group was significantly greater (87 % vs. 73 %).

Unpublished Studies

The Cornell Study

Upon the urging of interested parents, Dr. Maureen Packard of Cornell University in New York City agreed to perform a randomized prospective controlled study (Packard 2000). Children were randomized to immediate or delayed (6 months later) treatment with HBO (the delayed treatment group served as a crossover control group). Age range was 15 months to 5 years (average 30 months) with moderate to severe CP and patients were given forty 1-h sessions at 1.5 ATA, once a day, 5 days a week for 4 weeks. The study population included 26 children with cerebral palsy secondary to prenatal insults, premature birth, birth asphyxia, and postnatal hemorrhage. Nine patients presented with cortical visual impairment. Assessments were the Bayley II (cognitive), Preschool Language Scale, Peabody Motor Scale, and Pediatric Evaluation of Disabilities Inventory (PEDI), a parental report of specific skills including mobility, self-care, and social interaction. Final assessments were available on 20 subjects. The only side effects of the study were barotrauma in nine children, requiring placement of ventilation tubes or myringotomies. One child in the immediate HBOT group "developed complex febrile seizures and was dropped from the study." Two of 14 subjects in the delayed group developed seizures "and could not participate." Apparently, the seizures developed during the control wait period pre-HBOT.

Assessments were performed at four time points: enrollment (T1), after the immediate group had received treatment (T2), prior to the delayed groups" HBO therapy 5 months after enrollment (T3), and after the delayed groups' treatment (T4). There was a significant difference ($p < 0.05$) in the improvement of scores on the mobility sub-domains for the time period T2 minus T1 in favor of the immediately treated group. For the period T4 minus T3 there was a trend favoring the recently treated delayed group and a trend in the social function subdomain in the more recent treated group. Parental diaries over the month of treatments demonstrated 83 % improvement in mobility, 43 % increase in attention, and 39 % increase in language skills. Overall, 91 % experienced some improvement in mobility, 78 % in attention, 87 % in language, and 52 % in play. One family saw no improvement and six families minimal improvement (30 %). Five families (22 %) reported major gains in skills, and 11 families reported modest gains (48 %). Four of the nine children with cortical visual impairment had improvement in vision noted by families, vision therapists, and ophthalmologists. There was no statistical difference in Peabody or Bayley II scores on blinded assessment.

Conclusions at 6-month post-interview were that changes in spasticity may diminish over time after HBOT while improvements in attention, language, and play were sustained. "This increase in attention is particularly important for children must be aware' in order to learn. This represents a direct impact on cognitive functioning. The main differences between HBO and traditional therapies are the rapid gains over time and the impact on cognitive skills, which, in general are not improved by physical, occupational and speech therapies." Results of this study have only been published on a website after presentation at an HBO conference in Graz, Yugoslavia (Packard 2000).

Comparative Effectiveness Studies

Studies of the use of mild HBO, hyperbaric air, supplemental oxygen, and higher pressures of HBO continued despite the seemingly controversial results of the Collet study. At the 2003 3rd International Symposium on Hyperbaric Oxygenation and the Brain Injured Child, a variety of these studies were presented from around the world. While the studies were of varied design rigor, the results were similar, showing benefit of HBOT in CP, regardless of the lower dose of HBOT employed. The most significant study to date, however, reviewed both published and unpublished studies of

HBO in CP and compared published studies using the Gross Motor Function Measure (GMFM) in HBO to traditional accepted therapies that used the GMFM (Senechal et al. 2007). Compared to intensive physical therapy, dorsal rhizotomy, strength training, electrical stimulation, intrathecal baclofen, family-centered functional therapy, equine therapy, Bobath physical therapy, and other types of physical therapy HBO showed faster and more impressive improvements. Moreover, HBO was the only therapy to improve cognition and language. This study alone refutes the errant conclusion of the Collet study that the improvement in both groups of children was due to a parent-participation effect. The parent-participation effect as well as other "placebo"-type effects, such as surgery, is clearly present in every one of the studies and therapies reviewed by Senechal. Such a dramatic effect with HBOT that simultaneously improved cognition and language is consistent only with a biological cause–effect relationship of HBO on CP and the entire brain.

Recent Studies (Since 2007)

In 2012, Lacey et al. conducted a randomized prospective "controlled" trial of HBOT in CP children which was prematurely terminated for "futility." The study was similar to the Collet trial in that it was another multi-dosing study (not a true controlled study), but used hyperbaric oxygen versus hyperbaric hypoxic air (14 % oxygen at 1.5 ATA). Both groups received forty 1 h treatments at depth, once/day, 5days/week with compression and decompression on air. It employed an aggressive primary endpoint of a 5 % increase in GMFM-88 or 66, as well as secondary endpoints of improvement in the PEDI and Test of Variables of Attention (TOVA). A stopping rule for efficacy was set in advance, but not one for futility. At the second interim analysis that included 46 patients "the conditional probability of obtaining a difference between groups if the study continued to the end was only between 0.5 % and 1.6 %" so the study was stopped. The results at that point showed no change between groups, but a 1.5 % absolute increase (3.8 % of baseline score) in the HBO group and 0.6 % increase (1.5 % of baseline score) in the HBA group on the GMFM-88. In other words, the effect in the HBO group was more than double the effect in the "control" group.

Simultaneously, there were significant improvements in both groups on the PEDI that were similar in magnitude to the Collet PEDI results. In addition, the GMFM-66 increases were 1.2 points absolute (3.0 % of baseline) and 1.1 points absolute (2.7 % of baseline) in the two groups, respectively, with p values that approached significance (0.057 oxygen group, 0.074 hypoxic air group). Both the GMFM-88 and 66 improvements in Lacey et al. (2012) were less than those achieved in Collet et al. (2001), but very similar to the effect of other therapies used for CP (Senechal et al. 2007). This muted response in Lacey et al. (2012) may be explained by inclusion of dissimilar CP patients in the two studies: subjects in Collet et al. (2001) had to have evidence of perinatal hypoxia and excluded subjects with postneonatal onset CP, while subjects in Lacey et al. (2012) did not have to have neonatal hypoxia and did not exclude subjects with postneonatal onset CP. It appears the futility of stopping decision was based partly on a design flaw that was looking for a large and unrealistic difference between two doses of HBO, a pseudo-control group and a second dose of HBOT. Mukherjee et al. (2014) extended the findings in their earlier study (Sethi and Mukherjee 2003) with a non-randomized unblinded controlled study comparing standard intensive rehabilitation versus three different doses of hyperbaric oxygen therapy: 1.3 ATA air, 1.5 ATA oxygen, or 1.75 ATA oxygen, each for 1 h/day (90 min total treatment time), 6 days/week, for 40 treatments. GMFM-66 was measured pre and 2, 4, 6, and 8 months after beginning treatments. Forty percent of the children had "minor to moderate epilepsy" and 50 % of them were on anticonvulsants which were increased "marginally" during HBOT. The results showed that all four groups significantly improved over the course of the study, but the hyperbaric groups improved significantly greater and faster, consistent with the results of Collet. All three hyperbaric groups increased nearly one-half of a GMFM level on the longitudinal GMFM curves, uncharacteristic of and inconsistent with the natural history of CP. There was a slight dose–response effect (greater effect with increasing doses of oxygen and pressure), yet there was no significant difference between the three hyperbaric groups. The hyperbaric groups showed continued significant increases through the follow-up period with overall improvement rates from the beginning of the study equivalent to those HBOT rates published in Senechal's review and greater than other therapies for CP using the GMFM. No side effects were recorded in the study except for three patients with middle ear barotrauma. This was surprising given that 40 % of the subjects had epilepsy.

The final study, Asl et al. (2015), is a SPECT brain imaging study on 11 CP patients with perinatal asphyxia, four of whom were administered HBOT. HBOT was delivered at 1.75 ATA/60 min, once/day, 5 days/week for 40 treatments. Two of the four patients experienced significant improvement in SPECT, ages 7 and 12, while the 24- and 27-year-old patients did not. No other outcomes were measured.

Side Effects

The most common side effect in all of the above studies was middle ear barotrauma with rates as high as 50 % in one study (Collet et al. 2001). Pressure equalization tubes were inserted in 58 % of the Collet study children (Muller-

Bolla et al. 2006). The second most common side effect in the Collet study was pharyngitis which was seen in 22 % of the children. New onset seizures or exacerbation of seizures were seen in one treated patient in the Packard study ("complex febrile seizures"), at least one patient in Chavdarov's study and some of the patients in the Machado study. However, on follow-up in Machado's study parents reported "reduced frequency of seizure activity," Seizures were not reported in any of the more detailed and rigorous studies. While there does not appear to be an ability to predict sensitivity to oxygen (seizures) middle ear barotrauma is a largely avoidable side effect that is dependent on technique. In our very early experience treating CP, 1992–1998, middle ear barotrauma was common, but as our experience accrued with treating children with neurological disorders this has become a rare occurrence. The summary experience from the above studies is that HBOT in CP is a low-risk treatment.

The exception to this experience is the report of two purported complications of HBOT by Nuthall et al. (2000). The report consists of a child with an episode of vomiting and aspiration while in a hyperbaric chamber during treatment. Following the acute episode he was found to have "free gastroesophageal reflux with aspiration" on a feeding study. The second case involved a child undergoing HBOT who contracted a rapidly progressive parainfluenza type 3 infection with respiratory failure, seizures, and idiopathic thrombocytopenic purpura. During his critical illness, he suffered an acute middle cerebral artery stroke. Echocardiogram documented a patent foramen ovale with bidirectional flow. As pointed out in a rebuttal letter to the editor by Harch et al. (2001), the scientific explanations provided by Nuthall et al. were insufficient to attribute the complications to the HBOT. Harch et al. pointed out that their three authors had over 35,000 HBO treatments of brain injured children without any such complications. Moreover, they are complications never before seen in hyperbaric medicine. They recommended that proper medical evaluation and attendance of treatment was an important factor in delivering safe HBOT to children with neurological disorders.

To date, countless numbers of children with CP have been successfully treated with HBO worldwide. The studies with "negative" results, no difference between groups, are studies that compared multiple doses of HBOT. Neither of these (Collet et al. 2001; Lacey et al. 2012) have had true control groups. Both are multi-dose HBOT studies. In Collet et al. (2001) both groups improved significantly and at a greater rate than has been achieved by multiple other therapies for CP, and in Lacey et al. (2012) both groups achieved results equivalent to other therapies for CP. The Lacey et al. (2012) study was confounded by having studied a pathologically different group of CP children than Collet. Regardless, the net effect is one of benefit of HBOT for CP children using multiple different doses of HBOT.

The medical and scientific community, however, continues to be misled by a misunderstanding of the science of HBO and its effects on chronic brain injury. In 2007, the scientific underpinning of HBO in chronic brain injury was partially elucidated in a study that represents the first ever improvement of chronic brain injury in animals (Harch et al. 2007). This study demonstrated in a model of chronic traumatic brain injury that HBO could improve cognition and blood vessel density in a damaged hippocampus with a low-pressure HBO protocol originally employed on chronic trauma, stroke, CP, and toxic brain injury patients in the early 1990s. The unusual nature of the study was its retrograde proofing of concept in animals after 18 years of application of low-pressure HBO to chronic human brain injury. Since HBO's effects on acute and chronic pathophysiology documented in this text and the scientific literature are generic effects that cross species boundaries, they apply to patients with other types of chronic brain injury such as CP. What is most important is that these beneficial effects have been extended to children with cerebral palsy at both the doses used in the animal study (1.5 ATA) and in a wide range of adult neurological disorders (1.5 ATA) as well as at much lower doses, including compressed air. Examples of the effect of HBO on brain blood flow and metabolism that is responsible for the observed clinical effects can be seen in the cases below treated in New Orleans by this author over the past three decades.

Case Reports

Patient 1: Cerebral Palsy

The patient is a 2-year-old boy whose twin died in utero at 14 weeks. He was delivered at term by vacuum extraction and developmental delay was detected at the age of 4–5 months. He was diagnosed as a case of cerebral palsy. At 2 years of age SPECT brain imaging was performed and showed a heterogeneous pattern of cerebral blood flow. The patient underwent a course of twice daily, 5 days/week HBO treatments in blocks of 50 and 30 treatments. At the conclusion of treatments he showed improvement in spasticity, speech, chewing/swallowing, cognition, and ability to sit in his car seat and stroller for prolonged periods. Repeat SPECT brain imaging showed a global improvement in flow and smoothing to a more normal pattern consistent with the patient's overall clinical improvement. The two SPECT scans are shown side by side in Fig. 23.1. Three-dimensional reconstructions of the two scans are shown in Figs. 23.2 and 23.3.

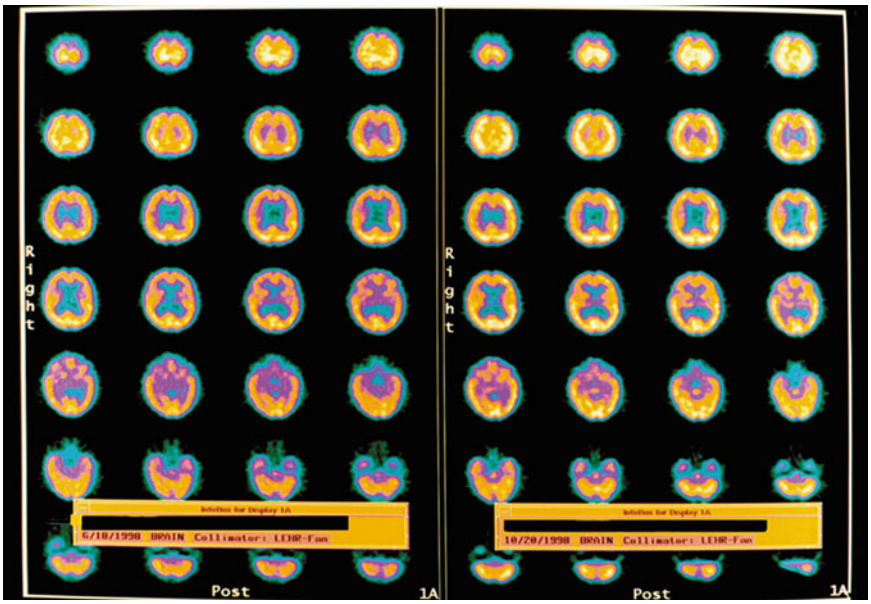

Fig. 23.1 SPECT brain imaging transverse images of baseline pre-HBOT study on the left and after 80 HBO treatments on the right. Note the global increase in flow and change from heterogeneous to the more normal homogeneous pattern. Slices begin at the top of the head in the upper left corner and proceed to the base of the brain in the lower right corner of each study. Orientation is standard CT: the patient's left is on the viewer's right and vice versa with the patient's face at the top and the back of the head at the bottom of each image. Color scheme is white, yellow, orange, purple, blue, and black from highest to lowest brain blood flow.

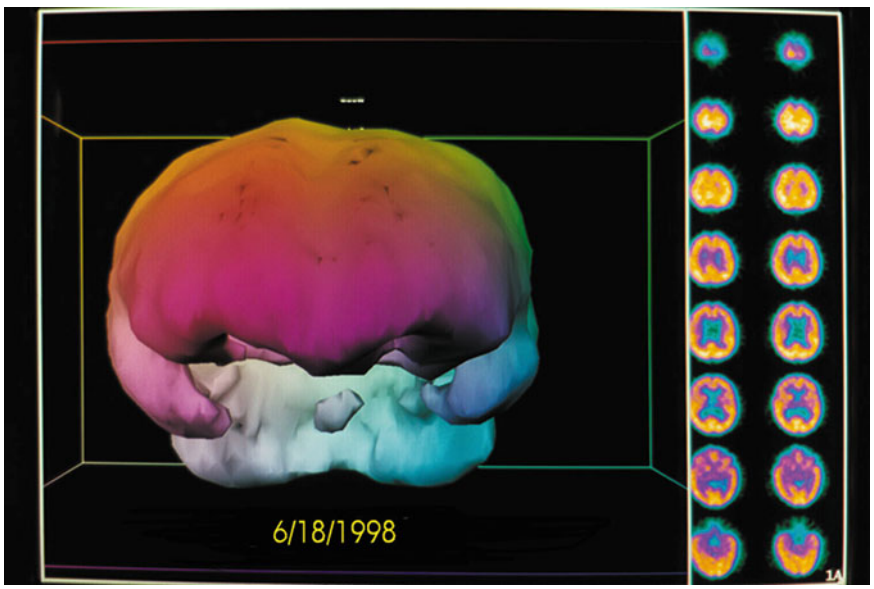

Fig. 23.2 Three-dimensional surface reconstruction of baseline SPECT study on left side in Fig. 23.1. Part of the transverse slices of the Fig. 23.1 baseline study are reproduced on the right side of this figure. The three-dimensional figure is reconstructed from the circumferential edge of each transverse slice. The three-dimensional figure is the face view of the patient. The large purple colored area in the middle of the figure represents the frontal lobes. The two inferior and lateral "bucket handles" are the temporal lobes. The eyes sit just below the frontal lobes and between the temporal lobes. The cerebellar lobes are the two rounded blue-white structures at the bottom of the figure in the back of the brain. The coloring is purely aesthetic/artistic and does not represent blood flow levels as do the colors on the slice images. Note reduction in flow to both temporal lobes, inferior frontal lobes, and the brainstem (central round white blue structure that appears to be "floating" between the temporal lobes below the purple frontal lobes).

Patient 2: Cerebral Palsy

The patient is an 8-year-old boy with a history of cerebral palsy. He had spastic diplegia secondary to premature birth from a mother with eclampsia. Patient was delivered by emergency Cesarean section at 27 weeks when his mother developed seizures. APGARS scores were 7 and 8. The patient spent 5 months in the hospital primarily because of feeding problems. The patient did not achieve normal milestones and developed infantile spasms at 2 years of age. Baseline SPECT brain imaging (Fig. 23.4) showed a mildly/moderately heterogeneous pattern and reduction of blood

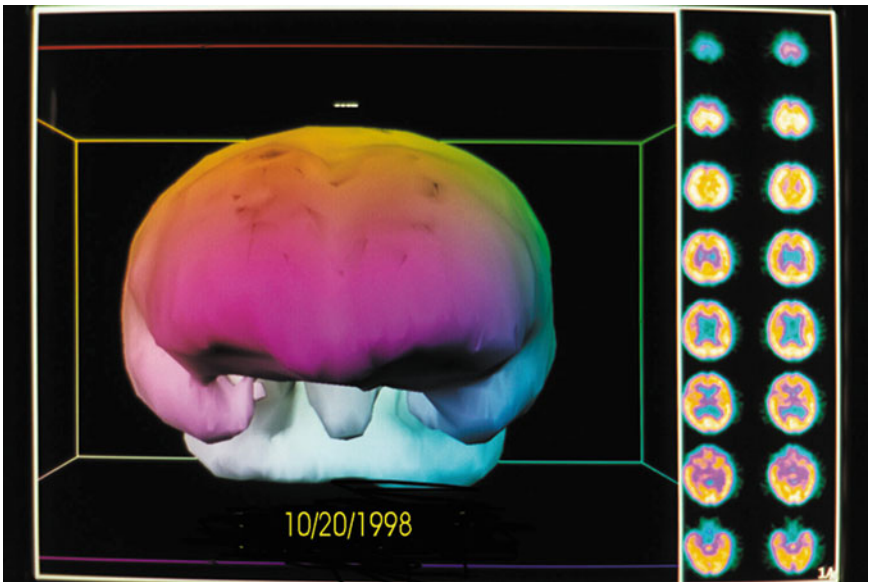

Fig. 23.3 Three-dimensional surface reconstruction of SPECT after 80 HBO treatments (right hand study in Fig. 23.1). Note the increased flow to the temporal lobes, inferior frontal lobes, and brainstem.

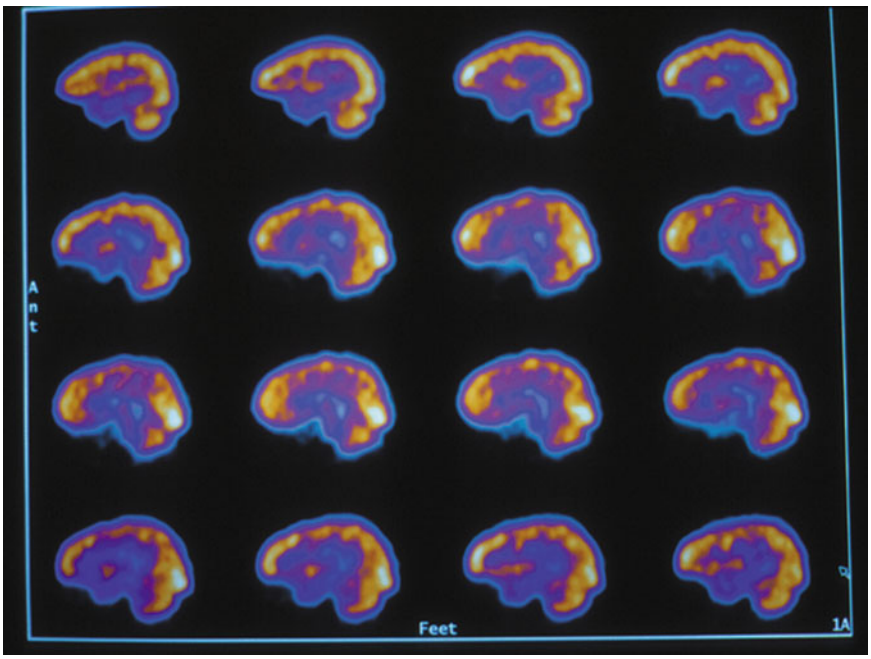

Fig. 23.4 Sagittal slices of baseline pre-HBOT SPECT brain imaging through the center of the brain. Note the heterogeneous pattern of blood flow. Slices proceed from the right side of the head in the upper left corner to the left side of the head in the lower right corner. The front of the brain (face) is on the left side and the back of the brain (back of the head) is on the right side of each slice.

flow. Three hours after a single HBO session at 1.5 ATA for 60 min, repeat SPECT showed global improvement and smoothing to a more normal pattern in Fig. 23.5. The patient underwent a course of 80 HBO sessions (1.5 ATA/60 min) over the next 6 months in two blocks of treatment (twice daily, 5 days/week × 40, then once-daily 5 days/week × 40), and showed improvement in his impulsive inappropriate behavior, motor function, vision, and constipation. Repeat SPECT brain imaging reflected these neurological gains (Fig. 23.6), showing generalized improvement in cerebral blood flow and pattern. Three-dimensional surface reconstruction of Figs. 23.4, 23.5, and 23.6 are presented in Figs. 23.7, 23.8, and 23.9, respectively. While there is a global increase in blood flow, the most significant relative increase in flow is to the temporal lobes as shown in the three-dimensional figures.

All SPECT brain imaging was performed on a Picker Prism 3000 at West Jefferson Medical Center, Marrero, Louisiana. All scans were identically processed and three-dimensional thresholds obtained by Phillip Tranchina. Pictures of the scans in the above figures were produced by 35 mm single frame photography under identical lighting and exposure conditions.

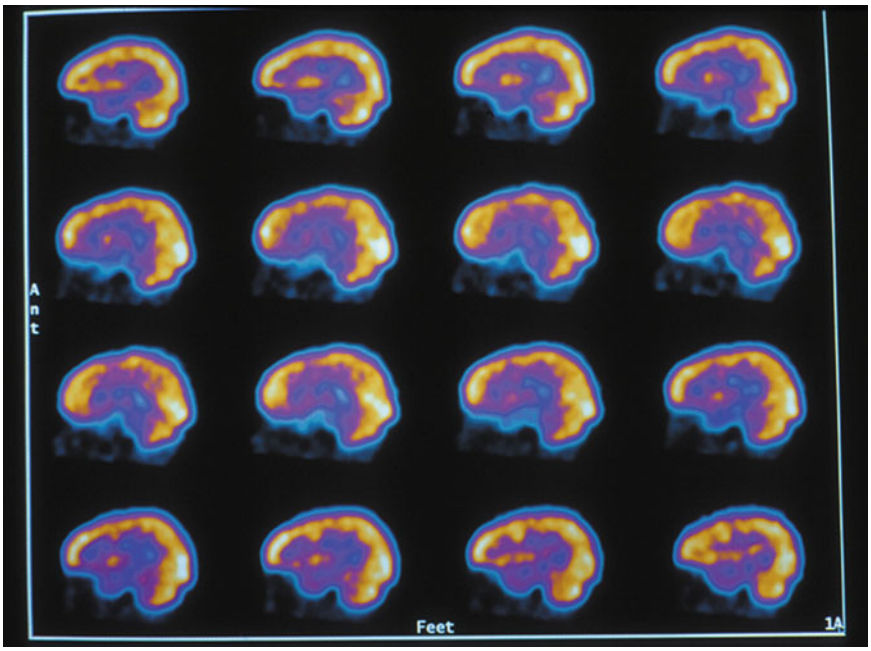

Fig. 23.5 Sagittal slices of SPECT three hours after a single 1.5ATA/60 min HBO treatment. Note the generalized increase in flow and smoothing to a more normal pattern.

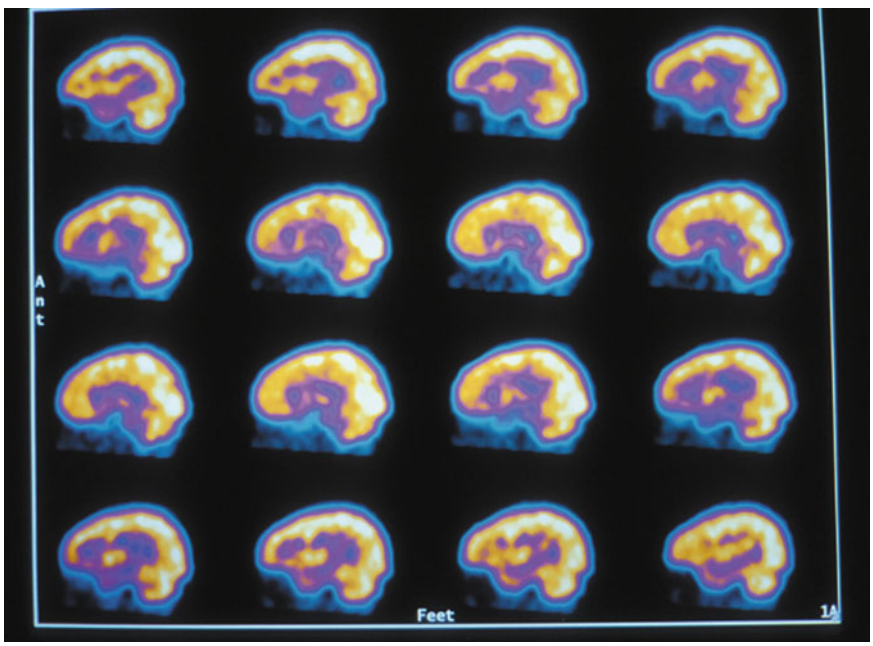

Fig. 23.6 Sagittal slices of SPECT after 80 HBO treatments. Note the marked increase in flow and smoothing of the pattern compared to the baseline in Fig. 23.4.

Conclusions

Cerebral palsy is a neurological disorder of diverse etiology. As a result, it is difficult to design trials with subgroups of patients with similar pathomechanisms. Regardless, the results of multiple studies on CP patients have been presented, including three controlled studies, and two rigorous multi-dosing studies mischaracterized as sham or placebo-controlled. Collectively, the data are showing faster, greater, and more durable improvements with a variety of doses of hyperbaric oxygen therapy, including compressed air, compared to therapies that are the standard of care for cerebral palsy. Some studies feature follow-up for as long as 6 months post-treatment and some have also documented sustained cognitive improvements. Positive outcomes have been demonstrated with as few as 20 treatments, but generally 40 or more treatments are recommended.

Controlled studies of HBO in CP should continue to refine and personalize the dosing of hyperbaric therapy for CP patients. However, it will likely take generations of

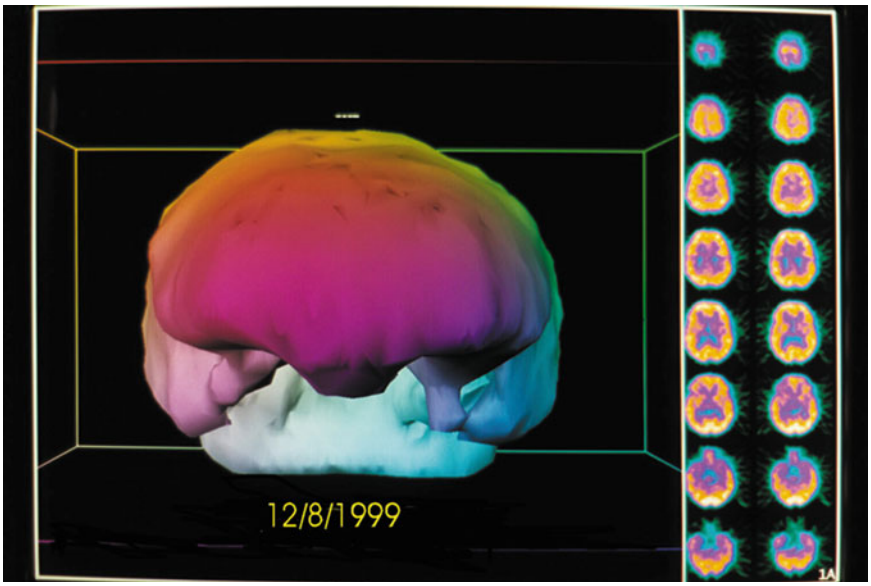

Fig. 23.7 Three-dimensional surface reconstruction of SPECT in Fig. 23.4. Note reduction in flow to the temporal lobes and coarse appearance of flow to the surface of the brain.

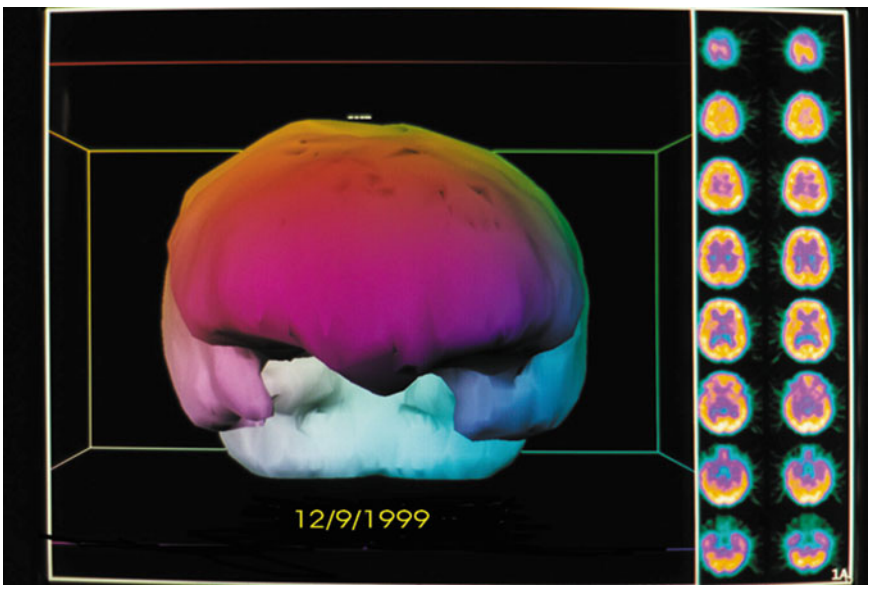

Fig. 23.8 Three-dimensional surface reconstruction of SPECT in Fig. 23.5. Note improvement in flow to the temporal lobes and slight smoothing of flow to the surface of the brain

properly conducted studies that incorporate the pressure and hyperoxic dosing concepts discussed above to reverse the imbedded negative sentiment in the pediatric neurology community (Novak and Badawi 2012; invited editorial to the Lacey 2012 study) toward hyperbaric oxygen therapy for CP. The likelihood of securing funding for such clinical trials is extremely low. The extensive positive data generated in the above clinical studies is sufficient to recommend hyperbaric oxygen therapy for CP. In a condition where there is no therapy to offer than can generate permanent improvements, HBO therapy is worth a trial. However, caution should be used in patients with seizure disorders and the patients watched carefully for manifestations of oxygen sensitivity/overdosing.

The concept of personalized medicine as described in Chap. 48 should be applied to HBO treatments in CP. One cannot recommend a standard protocol based on the above data, but the ideal treatment schedule should be determined for each patient including the pressure, dose, and duration of treatment. It may be possible to identify responders early on in the treatment. While molecular diagnostic procedures, genotyping, and gene expression studies may contribute to the evaluation and HBOT treatment of CP children in the future (Jain 2015), dosing of HBOT in CP still remains a clinical practice of medicine issue.

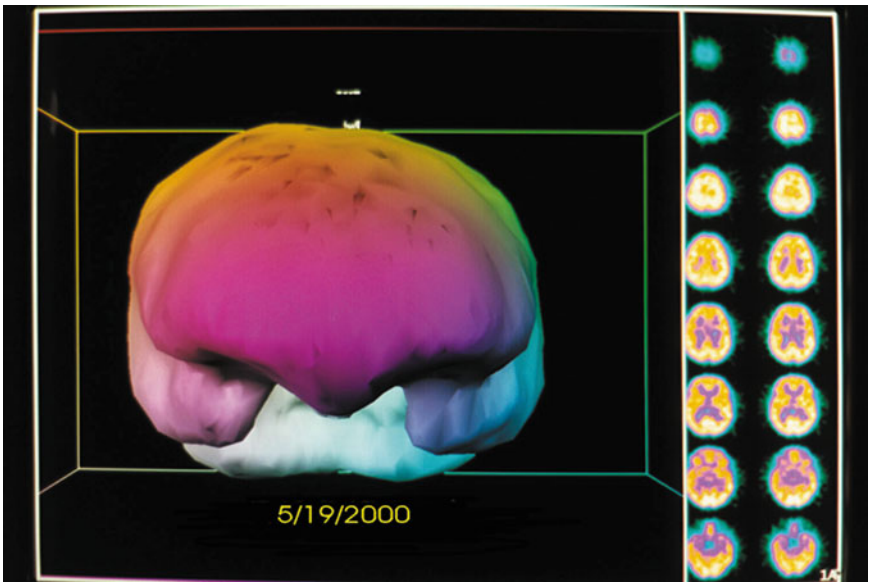

Fig. 23.9 Three-dimensional surface reconstruction of SPECT in Fig. 23.6. Note improvement in flow to the temporal lobes and slight smoothing of flow to the surface of the brain

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