Hyperbaric Therapy in Chronic Fatigue Syndrome

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ABSTRACT. The aim of this study was to determine if hyperbaric oxygen treatment (HBOT) could be used as adjunctive therapy and if HBOT could increase the quality of life in such a way that the functional status would improve in patients with an infection. A randomized, controlled trial was conducted on 15 *Mycoplasma* sp. infected CFS (CDC 1994) patients and 14 CFS (CDC 1994) patients with no evidence of a *Mycoplasma* infection were enrolled in a convenience randomization sample from our referral clinic. No statistical differences were found by use of univariate repeated measures although Bodily Pain as measured by the SF-36

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seems to decrease after hyperbaric therapy (Greenhouse-Geisser: p = .010). Trends were found using paired t-testing for *Mycoplasma* infected CFS patients. The general perceived fatigue seemed to decrease after hyperbaric therapy (General Fatigue: p = .06). Directly after one week of hyperbaric therapy general fatigue improved (p = .03) but there was a reduction of activity (reduced activity: p = .05) and general perceived health (general health: p = .04). One month later the physical role increased (Role-Physical: p = .07). Although more data is required to make firm conclusions, trends were found. Reduced fatigue, increased levels of activity and an improved reaction time improved significantly their quality of life and therefore, enhanced also their functional status and thus could be used as an adjunctive therapy. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com>*

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INTRODUCTION

Chronic Fatigue Syndrome (CFS) was first described in the 1930s and due to its definition by exclusion, its pathogenesis has been difficult to delineate. During the last few decades an increasing number of studies have started to unravel the pathogenesis of CFS. Currently the etiology is not known and no definite pathological abnormalities have been identified, therefore CFS is still called a syndrome and not a disease or group of diseases.

The controversy around this syndrome is intense with the overriding theme being whether its origin is physical or psychological. Interestingly this very same debate has taken place for many other chronic diseases in which initially no objective abnormalities were found followed by findings which clearly establish a physical/organic basis to the disease, leading to their wide acceptance.

Up until now, many therapies have been investigated in this population with different results (1). One of the most promoted therapies seems to be 'Cognitive Behavioral Therapy (CBT) with Graded Exercise' (2). The restricted lifestyle of CFS patients has led to the suggestion that a reduction in exercise capacity contributes and prolongs their illness. It is for this reason that exercise-training programs are added to

the treatment of CFS-patients (2). Different ailments, however, inhibits wide spread application. First of all, CBT has not been adequately assessed for severely affected CFS patients (3). In fact, CBT seems applicable only when a Karnofsky Performance Score (KPS)-threshold of 70 is reached (4,5). The Karnofsky Performance Score indicates functional disability in different populations and is used as a communication tool in CFS. A KPS of 70 means that the CFS patient "cares for him/herself but is unable to carry on normal activity or do active work." This threshold (70) is in contrast with the overall score of the CFS population which is 60-65. A person with a KPS of 60-65 "requires occasional assistance but is able to care for most needs." Secondly, CBT is characterized by a high dropout rate (6).

So, in order to bring CFS patients to a threshold of 70 and in order to bring CFS patients in the ability to start up an exercise program, different strategies should be used. While CFS patients do have abnormal immune parameters which indicate infections agents (7), hyperbaric oxygen therapy could be considered. By applying HBOT, the quality of life should be influenced in those patients with distorted immune parameters. A higher quality of life suggests a higher functional status. If patients increase their area of control by more activity or less fatigability, such as more walking around or leaving the home, leading to more independence, this implies a higher functional status.

Rationale for the Use of Hyperbaric Therapy in CFS

The immune system, wound healing, and vascular tone are all affected by oxygen supply. Oxygen alone has little direct antimicrobial effect, even for most anaerobes (8) like *Mycoplasma* infections. It is, however, a crucial factor in immune function. Neutrophils require molecular oxygen as a substrate for microbial killing. The oxidative burst seen in neutrophils after phagocytosis of bacteria involves a 10 to 15-fold increase in oxygen consumption (9). Here oxygen serves as a substrate in the formation of free radicals, which directly or indirectly initiate phagocytic killing. This endogenous antimicrobial system virtually ceases functioning under conditions of hypoxia (10). In short, increasing the oxygen level in tissue can allow restoration of white blood cell function and thus the return of adequate antimicrobial action. However, whether this is applicable in a normal physiological system or some other process may be involved is not known.

History of Hyperbaric Therapy

The use of hyperbaric air therapy was apparently attempted before anyone knew of the existence of oxygen (11). A physician named Henshaw first attempted to treat patients in a chamber with altered air pressure about 300 years ago (12).

Hyperbaric oxygen therapy (HBOT) involves intermittent inhalation of 100% oxygen under a pressure greater than one atmosphere. Initial widespread enthusiasm for HBOT led to its inappropriate use, resulting in a backlash against the use of HBOT (12). More recent and reputable studies have demonstrated that the technique has a role in treating specific illnesses (11).

The Undersea Medical Society that evaluates clinical applications of HBOT has categorized disorders of which it is or may be useful (11). Table 1 gives an overview of the different treatment areas suggested for HBOT: category 1 is widely accepted and category 4 has little evidence to support its use. CFS patients with chronic bacterial infections are categorized as an adjunctive therapy by the Undersea Medical Society.

Complications and Side Effects of HBOT

The complications of HBOT are related to the changes in barometric pressure and oxygen toxicity. Patients can receive mild inner ear dis-

TABLE 1. Possible disorders treated by HBOT by the Undersea Medical Society (Adapted from Gunby, 1981)

Category 1 (Vast evidence)	Category 2 (Adjunctive usefulness)	Category 3 (Controversy)	Category 4 (Remote evidence)
Decompression sickness	Soft-tissue radionecrosis	Bone grafts	Arthritis
Acute gas embolism	Actinomycosis	Acute carbon tetrachloride poisoning	Breast firming and enlargement
Gas gangrene	Bacterioides infections	Extreme hemodilution in cardiac bypass	Emphysema
Soft-tissue infection	Ischemia	Diabetic retinopathy	Loss of normal hair color
Compromised skin grafts or flaps	Crush injury	Frostbite	Multiple sclerosis
Acute carbon monoxide poisoning	Head and spinal cord trauma	Acute or hemorrhagic cerebrovascular accident	Hypertension
Cyanide poisoning	Acute cerebral edema	Migraine headache	Loss of sexual vitality
Smoke inhalation	Intestinal obstruction	Nonjoined fractures	Skin wrinkles
Exceptional blood loss	Refractory osteomyelitis	Nonhealed fractures	
	Renal artery insufficiency	Abscesses	
	Nondiabetic retinopathy	Lepromatous leprosy	
	Ulcers	Meningitis	
	Acute thermal burns	Sickle cell hematuria	
	Re-anastomosis of limbs	Cerebral arterial insufficiency	
		Chronic stroke	
		Ulcers	

comfort that may occur by using certain maneuvers. The most common complication is middle ear or sinus trauma (9) due to the change in pressure. Any air filled cavity that cannot equilibrate with ambient pressure, such as the middle ear is subject to deformity and barotraumas during pressure changes in HBOT. Other complications sometimes observed at this pressure can include nausea, tooth and sinus pain and blurred vision (9).

Hypotheses

This controlled pilot study evaluates the utility of HBOT in CFS patients infected with *Mycoplasma hominis*. In other words, can HBOT improve the quality of life of this subgroup of CFS patients as investigated by validated psychological questionnaires? If the quality of life improves, patients may reach a KPS-threshold of 70 and additionally, attend CBT and graded exercise to improve their functional status.

PATIENTS AND METHODS

Patients

Fifteen patients diagnosed with CFS (13) carrying an infection (*Mycoplasma hominis*), detected by PCR, were eligible for the study. Another fourteen CFS-patients (13) served as controls of which no one had a *Mycoplasma* infection or any other chronic systemic anaerobic infection. Patient participation relied on convenience for the patients and was chosen at random from a database of CFS-patients.

Taking oral or IV antibiotics, pregnancy or breast feeding, claustrophobia, upper respiratory tract infections, sinusitis, fever, pneumothorax, barotrauma of the ear and hyperinflation of the airways were the exclusion criteria.

All subjects signed an informed consent form.

Design and Procedures

HBOT took place in The Diving and Hyperbaric Medical Centre in Zeebrugge (Belgium) during November and December 2000 and was given for two hours per day for one week. Assessments were taken immediately before (baseline), after the procedure (1 Wk) and 1 month (1 Mh) following HBOT therapy.

Hyperbaric oxygen was administered in a multi-person chamber. These chambers are large tanks accommodating 2 to 14 people. They are usually built to achieve pressure up to 6 atmospheres and have a chamber lock-entry system that allows personnel to pass through without altering the pressure of the inner chamber. Patients could be directly cared for by medical staff within the chamber. The chamber was filled with compressed air and the patients breathed 100% oxygen through a face mask.

The protocol was approved by the ethics committee of the Belgium Armed Forces.

Assessments

California Computerized Assessment Package (CalCAP): Reaction times were collected on a personal computer using the measures developed and described by Miller et al. (14,15) which includes four measures of simple reaction time and six measures of choice reaction times (Go-No Go; Lexical Discrimination; Sequential Memory, Visual Distraction, Response Reversal and Form Discrimination). For all tasks, target stimulus materials appeared in a box in the center of the computer screen. The CalCAP was administered directly before and 1 month after the HBOT therapy.

Medical Outcomes Study SF-36: The SF-36 assesses functional status and well-being or quality of life. Its psychometric properties are well characterized; it has been documented to have reliability and validity in a wide variety of patient populations (16-18).

The SF-36 contains 8 subscales: physical, emotional, social, and role functioning, body pain, mental health, vitality, and general health. Higher scores indicate better health and less body pain. Scoring of the SF-36-item was performed as describing the manual (19).

General Health Questionnaire (GHQ-30): The GHQ is a well-known and extensively validated screening questionnaire for functional psychiatric illness (20). It has been tested and validated in a number of cultures and languages (21). Both GHQ-30 score (20) and the revised GHQ-30 score (21) were encoded. The score ranges from 0 to 30. A high score describes high probability of functional psychiatric illness.

Multidimensional Fatigue Inventory (MFI-20): The MFI-20 is a self-report instrument. The current version contains 20 statements which covers different aspects of fatigue. These items are organized in five scales: General fatigue, Physical fatigue, Reduced activity, Reduced motivation, and Mental fatigue. The scores can range from 4-20 (22).

The validity and reliability of these scores were investigated by Smets et al. (22).

Statistical Methods: The main research hypothesis relates to the difference in response profile to hyperbaric treatment between *Mycoplasma hominis* infected and non-*Mycoplasma* infected CFS patients. As observations were made for the same patients over time, a univariate repeated measures ANOVA was performed on the data. The within group factor assessed was time which was assessed at three levels: baseline, 1 week (Wk) and 1 month (Mh). The between group factor was *Mycoplasma hominis* (presence or absence). A full factorial analysis was performed with age as covariate. The effect of particular interest was the interaction between the two major factors: infection with *Mycoplasma hominis* and time. Corrections for lack of sphericity were made where appropriate, using the Greenhouse-Geisser correction factor. Treatment effectiveness was assessed by ANOVA and paired t-tests between the pre- and posttreatment observations. The data was checked for normality and homogeneity of variance. All computations were performed using the SPSS™ statistical software package (SPSS for Windows, Release 10.07,1999, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Twenty-nine subjects were assessed in this controlled pilot study with a mean age of 42 (±13) years. Ten (34.5%) were men and nineteen (65.5%) were women. Table 2 shows the demographics of the two groups. The mean age for the infected CFS patients was 35.0 years (±12.15) and 48.9 years (±8.84) for those not infected. Age was thus statistically different between the two groups and was controlled for during subsequent analyses. There was no difference in functional status before the start of the program (data not shown).

TABLE 2. Demographical variables of the different subgroups

	N	Age Years (SD)	Onset of complaints Years (SD)	% Females
Mycoplasma hominis	15	35.3 (12.15)*+	8.0 (5.54)°	60
No mycoplasma	14	48.9 (8.84)*+	8.1 (6.69)°	71.5

* t-test
+ Statistically significant: $p < .001$
° Mann-Whitney U test

Multidimensional Fatigue Index

Using univariate repeated measures (ANOVA), no statistically significant difference in any measure was found for CFS patients with *Mycoplasma hominis* (data not shown). Similarly, using paired t-testing between baseline and 1 Wk no differences were found. The perceived general fatigue diminished immediately after the HBOT (Table 5; $p > .001$) and was still stable 1 month after HBOT. Activity did increase directly after the HBOT suggesting more physical capacities (Table 5; $p > .001$). No differences were found regarding CFS patients without *Mycoplasma* infection (data not shown).

General Health Questionnaire

Using univariate repeated measures (ANOVA) or using paired t-tests, no statistically significant difference was found for CFS patients with or without *Mycoplasma hominis* (data not shown).

Medical Outcome Study SF-36

For CFS patients with *Mycoplasma hominis*, Bodily Pain is influenced by HBOT (Table 3 and Figure 1). Directly after the HBOT there seems to be an increase that stabilizes again after 1 month (Greenhouse-Geisser; $p > .001$).

Trends also exist for Role-Functioning (Tables 4 and 5). A higher score indicates better role-physical functioning as seems the case in our sample ($p > .001$).

General health perceptions improved, indicating better general health perceptions (Table 5). CFS patients without *Mycoplasma hominis* infection report better mental health (Table 6; $p > .001$) directly after the HBOT.

California Computerized Assessment Package (CalCAP)

Trends appear using both univariate repeated measures (ANOVA) and paired t-tests. Form discrimination (Table 5; $p > .001$) and Word discrimination (Table 3; $p > .001$) improve after HBOT in CFS patients with a *Mycoplasma hominis* infection. In the group without *Mycoplasma hominis* infection, no trends or statistically significant differences are apparent (data not shown).

TABLE 3. Significance of differences between the different subgroups over time (univariate repeated measures ANOVA–interaction test)

		Mean (SD) Baseline		Mean (SD) 1 Week		Mean (SD) 1 Month		p
		Mycoplasma hominis	*No Myco*	*Mycoplasma hominis*	*No Myco*	*Mycoplasma hominis*	*No Myco*	
Multidimensional Fatigue Index	General Fatigue	18.7 (1.8)	18.7 (2.4)	16.1 (4.5)	17.5 (3.1)	17.6 (4.5)	16.8 (4.2)	.274
	Physical Fatigue	17.6 (2.1)	17.9 (2.9)	16.2 (3.9)	17.3 (2.6)	17.5 (3.9)	17.0 (3.8)	.864
	Reduced Activity	15.8 (2.2)	16.8 (3.9)	15.6 (3.4)	16.8 (3.5)	16.0 (3.5)	17.5 (3.1)	.182
	Reduced Motivation	12.7 (4.6)	12.1 (5.1)	12.8 (4.1)	11.7 (4.2)	12.0 (4.1)	13.1 (4.2)	.672
	Mental Fatigue	15.1 (3.7)	15.3 (4.4)	15.7 (3.7)	14.2 (5.2)	15.1 (3.7)	13.8 (5.3)	.671
General Health Questionnaire	GHQ-30	12.1 (6.2)	8.9 (8.0)	8.9 (6.9)	7.5 (7.7)	9.5 (6.9)	7.6 (7.7)	.671
	CGHQ-30	17.3 (4.9)	15.1 (7.1)	15.7 (5.5)	12.4 (8.3)	16.4 (5.6)	13.0 (7.8)	1.000
SF-36	Physical Functioning	36.5 (11.9)	28.7 (6.4)	37.5 (11.5)	29.8 (7.1)	36.4 (11.6)	31.0 (8.3)	.514
	Role-Physical	29.9 (7.7)	30.6 (10.3)	28.6 (5.7)	31.3 (9.6)	33.8 (5.7)	30.1 (9.9)	.079
	Bodily Pain	36.9 (10.2)	34.9 (8.1)	38.7 (9.8)	32.7 (11.0)	37.3 (9.8)	35.5 (12.0)	.010
	General Health Perceptions	27.3 (4.5)	26.1 (4.4)	28.9 (5.7)	27.1 (6.1)	28.3 (5.7)	27.7 (5.8)	.966
	Vitality	33.6 (8.9)	33.8 (6.5)	34.5 (11.8)	35.1 (10.8)	36.5 (11.8)	39.4 (14.3)	.779
	Social Functioning	30.5 (10.7)	28.0 (6.2)	33.0 (13.7)	27.2 (7.9)	33.6 (13.7)	29.9 (11.0)	.502
	Role-Emotional	41.1 (16.2)	40.0 (16.8)	37.5 (17.0)	37.5 (16.3)	44.9 (17.1)	40.1 (18.1)	.510
	Mental Health	42.7 (9.3)	39.7 (9.5)	42.2 (10.3)	41.6 (10.6)	43.1 (10.3)	44.5 (11.7)	.687

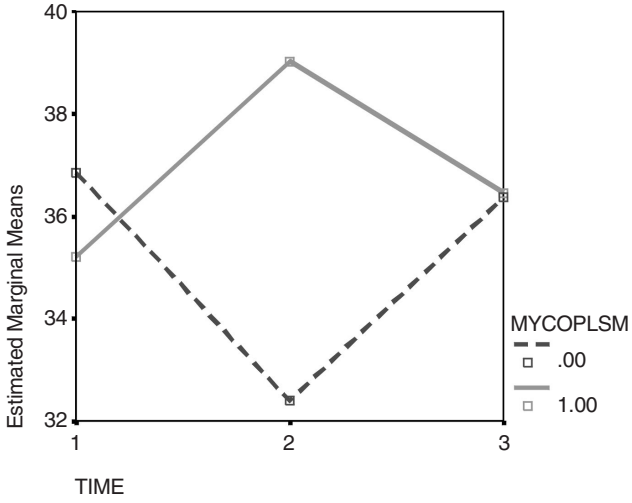
* Statistically significant: $p < .001$

DISCUSSION

Although limited in sample size, this pilot study shows that the infected CFS patients report some changes during and after hyperbaric therapy. Oxygen treatment seems to provoke changes in the perceived fatigue, physical activity and general health perceptions in CFS patients with *Mycoplasma hominis* directly after the HBOT.

CFS patients with *Mycoplasma hominis* increased their activities (physical or mental) and still felt less fatigued. This effect could be due

FIGURE 1. Bodily pain at baseline, 1 Wk and 1 Mh



to an enhanced oxygen supply although it was not observed in the CFS patients without the infection. However, the physiological mechanisms inducing these changes are not known. Similarly, the increase of the experienced bodily pain in the CFS patients with *Mycoplasma hominis* may be due to many different unknown physiological changes. Interestingly, the increase in Bodily Pain returned toward pre-treatment levels after the HBOT. This change may be an indicator that HBOT therapy for a week may be too little, however, the real reasons are unknown. Improvements in cognitive and motor functioning were demonstrated and are consistent with the findings of Neubauer et al. (23) who considered HBOT to be valuable in anoxic encephalopathy and possible other traumatic dysfunctions of the central nervous system.

Patients not infected with chronic systemic infections showed no improvements except for better mental health. How this change in mental health occurred is not known but may be associated with the increased attention given by the staff during the one week treatment period.

The pilot study differences suggest that HBOT may be used as an adjunctive therapy for CFS patients infected with *Mycoplasma hominis* although more research is needed. For instance, if HBOT was given longer than 1 week, would the differences be more pronounced?

In general, the recommendation of the Undersea Medical Society as described in Table 1, seems to stand. Although no physiological changes

TABLE 4. Significance differences between the different subgroups over time (univariate repeated measures)

		Mean (SD) Baseline		Mean (SD) 1 Month		P
		Mycoplasma hominis	*No Myco*	*Mycoplasma hominis*	*No Myco*	
Reaction Time Test	SRTR	51.3 (7.2)	42.1 (16.8)	49.7 (6.7)	43.2 (15.4)	.472
	SRTL	49.3 (12.9)	35.3 (22.3)	44.7 (12.4)	38.4 (13.6)	.175
	CRT	47.3 (11.7)	31.6 (21.6)	38.3 (18.3)	32.8 (21.6)	.158
	CRTS	47.2 (11.1)	44.3 (15.8)	46.8 (8.8)	41.9 (13.6)	.665
	CRTL	43.8 (10.2)	38.8 (14.3)	42.5 (11.8)	43.1 (15.1)	.059
	CRr2	53.1 (7.1)	44.9 (18.5)	54.0 (6.7)	47.5 (16.6)	.809
	CRTD	45.8 (9.7)	38.1 (11.7)	47.0 (10.5)	43.7 (12.3)	.421
	CRTR	49.0 (10.5)	42.9 (10.9)	48.5 (12.2)	43.9 (11.1)	.847
	CRTF	55.0 (7.8)	47.4 (11.9)	59.3 (5.4)	50.2 (10.1)	.130
	SRTr3	51.5 (9.3)	45.0 (16.6)	48.7 (16.7)	45.2 (15.5)	.503

ANOVA–interaction test of the reaction time test
* Statistically significant: p < .001

TABLE 5. Significant differences using paired t-tests for CFS patients with *Mycoplasma hominis*

	Mean (SD)	Mean (SD)	P
	Baseline	*1 Week*	
General Fatigue	18.67 (1.80)	16.10 (4.48)	.03
Reduced Activity	17.00 (2.20)	15.67 (3.46)	.05
General Health	27.26 (4.49)	28.90 (5.76)	.04
	1 Week	*1 Month*	
Role-Physical	28.60 (5.74)	33.84 (9.96)	.07
	Baseline	*1 Month*	
General Fatigue	18.67 (1.80)	17.6 (2.94)	.06
Reaction Time	55.00 (7.89)	59.31 (5.42)	.04

* Statistically significant: p < .001

TABLE 6. Significant differences using paired t-tests for non-infected CFS patients

	Mean (SD)	Mean (SD)	P
	Baseline	*1 Week*	
Mental Health	39.75 (9.54)	44.49 (11.68)	.07

* Statistically significant: p < .001

have been reported, positive changes in quality of life appear after one week of HBOT. Indeed, HBOT may not cure these CFS patients but instead may enhance their quality of life and serve as an adjunctive therapy for CFS patients with *Mycoplasma* infections. Reduced fatigue and increased levels of activity as well as an improved reaction time may well be enough to push these CFS patients from a KPS of 60-65 to the threshold of a KPS of 70. Therefore, HBOT could be the predecessor of CBT. Until now, CFS patients with a KPS < 70 fell off the wagon and were only able to follow medical treatment like antibiotics or symptom-relief-treatment.

This pilot study was designed as a descriptor of the changes produced by Hyperbaric Oxygen Therapy and as such has a number of limitations. The study was not designed to rule out any alternative etiological explanations of these changes. This study was prospective but required patients to interpret subjective feelings and/or changes in their bodies. Finally, the sample size was small and participation relied on convenience for the patients, even though they were selected on a random basis. Therefore, the conclusions have to be interpreted with caution.

CONCLUSIONS

To our knowledge, this is the first time that possible changes by HBOT were recorded in CFS patients. HBOT seemed to enhance quality of life in CFS patients with *Mycoplasma* infections by means of enhancing the perceived fatigue, physical activity and general health perceptions. Although these are preliminary data, HBOT seems a safe and effective adjunctive therapy when administered at least each day during one week.

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