Effect of normobaric and hyperbaric hyperoxia treatment on symptoms and cognitive capacities in Long COVID patients: a randomised placebo-controlled, prospective, double-blind trial

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Abstract
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Introduction: Long COVID syndrome is a major health issue. Multiple treatments have been proposed but efficacy is inadequately investigated. Hyperbaric oxygen therapy (HBOT) has been promoted based on a small number of publications. As there is potential for a placebo effect and the financial cost of HBOT is high, we sought to investigate the effects of HBOT in Long COVID in a randomised trial.
Methods: We randomised 101 patients into four treatment groups, receiving 10 sessions of oxygen 'treatment' inside a pressure chamber, according to one of four modalities: A – 100% oxygen at 253 kPa (2.5 atmospheres absolute); B – 40% oxygen at 253 kPa; C – 100% oxygen at 101.3 kPa (1 atmosphere absolute); D – 21% oxygen at 101.3 kPa. Groups B and C thus received a similar effective oxygen dose of 101.3 kPa. Quality of life symptom scores (Visual Analogue Scale; EQ-5D-5L, C19-YRSm), a 6-minute walking test and five neurocognitive tests were administered before and after the treatment series. At three months post-treatment, a telephone questionnaire probed for lasting effects.
Results: All groups were comparable with regards to demographics, Long COVID symptoms and severity. After treatment, there were no significant differences in subjective symptoms, functional scores, and cognitive performance between any groups. The response to treatment was highly variable, with some patients in even the 'placebo' group D reporting a significant improvement in their well-being. This was not reflected in any objective outcome scores. No subgroups of patients responded better to any of the treatments.
Conclusions: There was no significant effect from different doses of oxygen in a hyperbaric chamber. It is possible that the very modest improvements reported in other studies were due to a placebo effect. Claims that HBOT has a significant effect on Long COVID need further investigation before indiscriminately prescribing or promoting HBOT.

Introduction

From 30 January 2020 to the 5 May 2023, the World Health Organization (WHO) declared SARS-CoV-2 (COVID-19) a pandemic. Official figures mention 765,222,932 cases and 6,921,614 deaths worldwide during this period, most probably a vast underestimation. Among patients recovering from the acute phase, a certain percentage was observed to have persisting symptoms, and in September 2020, International Classification of Disease (ICD) codes were created for this 'Post-COVID Condition'. In October 2021, the WHO published a clinical case definition for Post-COVID Condition, based on a Delphi consensus method.[1]

A post-COVID condition case was described as a patient who has a) a history of probable or confirmed SARS-CoV-2 infection, presenting b) usually three months or more from the onset of COVID-19 disease, c) symptoms that last for at least two months that d) cannot be explained by an alternative diagnosis.

The consensus text further specified that: "*Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19*

episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children".[1]

Post-COVID Condition (better known by the general public as 'Long COVID syndrome') is considered a major health issue after the COVID-19 pandemic. Although many patients seem to improve after two years, many more remain severely handicapped in their family, social and professional life. The exact prevalence is unknown. While initial estimates in 2021 mentioned that up to 10–20% of patients have persisting symptoms,[1] two papers in 2022 estimated the prevalence at 12.7%[2] and 'up to 45%'[3] respectively; a subsequent review in 2023 mentioned 6–10%.[4] In any case, in view of the numbers infected with SARS-CoV2, the number of patients with Long COVID is staggering.

Core symptoms have been defined[2] and may be classified as cardiopulmonary symptoms (chest pain, difficulties with breathing, and pain when breathing), musculoskeletal symptoms (painful muscles), sensory symptoms (ageusia or anosmia, tingling extremities, lump in throat, and feeling hot and cold alternately), and general symptoms (heavy arms or legs, and general tiredness). Cognitive impairment ('brain fog'), although not mentioned as a core symptom in the Ballering paper,[2] has been reported in 16–23% of a group of 740 patients at a mean of 7.6 months from COVID-19 diagnosis.[5]

The mechanism of disease has not been identified, and multiple hypotheses have been formulated based on observed biochemical changes.[6] Multiple treatments have been proposed and are actively pursued by patients; however, the efficacy of these treatments remains low and proper scientific evidence is often lacking.

Hyperbaric oxygen therapy (HBOT) has been proposed for treatment of Long COVID syndrome since 2021 and has been widely promoted in the Long COVID patient population (by means of internet chat groups) based on a small number of publications. The first published study, by Robbins et al. in 2021, reported statistically significant and large to very large effects on fatigue and cognitive functioning, after only 10 HBOT sessions.[7] In 2022, two more studies reported 'important subjective improvement' after a short series of HBOT (10 sessions).[8,9] As the logistic and financial cost of HBOT is important and as there is a high potential for a placebo effect, we sought to investigate whether 10 treatments of HBOT provide significant improvement of the symptoms and cognitive capacities of these patients using a prospective, randomised, and blinded placebo-controlled design.

Administering a 'true' placebo (21 kPa [0.21 atmospheres] oxygen) inside a hyperbaric chamber is difficult to near impossible, as even a 'sham' compression to 130 kPa (1.3 atmospheres absolute [atm abs]) with air breathing effectively yields a partial pressure of oxygen equivalent to breathing 27% oxygen at 101.3 kPa (1 atm abs), and thus could have a therapeutic effect. Therefore, rather than trying to devise a 'perfect sham' we sought to determine if different levels of oxygenation at partial pressures of 21 kPa (0.21 atm abs), 101.3 kPa (1 atm abs) or 253 kPa (2.5 atm abs), given in various combinations of pressure and inspired oxygen fraction, could have different therapeutic effects, and if so, whether there is a role for increased pressure as well. The 'null hypothesis' was that no combination would yield a better result than 21 kPa (0.21 atm) inspired oxygen at 101.3 kPa (1 atm abs) ambient pressure.

Methods

The research protocol was approved by the Hospital Ethics Committee of the University Hospital Brugmann, Brussels (B0772022000037) on 12 April 2022.

Patients were first recruited among Belgian military personnel by means of a call for participation by email to all service personnel. This was our primary recruitment population, based on previous research[10] (H. Mazibas, doctoral thesis) having identified more than 350 Belgian military Long COVID patients. However, owing to a lack of sufficient participants from this source, a second round of recruitment was undertaken by seeking participants through various self-help groups online (mainly Facebook). After preliminary screening by means of a short questionnaire, patients were invited to select one of several pre-defined treatment periods of two consecutive weeks.

The week before the start of each treatment period, the eligibility of patients was verified during a medical consultation, as was the absence of contra-indications for pressure chamber treatment. Then, after having signed informed consent, patients' COVID history, initial and persisting symptoms and signs, and previous treatments tried were noted in an unstructured manner, and they were subjected to a series of objective tests and subjective evaluation questionnaires, as described below.

Next, they were randomised (1:1 allocation using a 4-block randomisation table generated in MS Excel 365) into four treatment groups and received 10 sessions of oxygen treatment inside a pressure chamber, according to 4 different modalities: A – 100% oxygen at 253 kPa (2.5 atm abs); B – 40% oxygen at 253 kPa; C – 100% oxygen at 101.3 kPa (1 atm abs); D – 21% oxygen at 101.3 kPa. Groups B and C thus received a similar effective oxygen dose of 101.3 kPa. All treatments lasted 95 minutes, with 15 minutes of (real or simulated) compression, 70 minutes of treatment and 10 minutes of (real or simulated) decompression.

Patients were blinded to the exact oxygen dose they received, and all were subjected to significant pressure variations in the beginning and end of each treatment session. Patients in groups A and B were treated in the hyperbaric chamber of the Centre for Hyperbaric Oxygen Therapy (CHBO) of

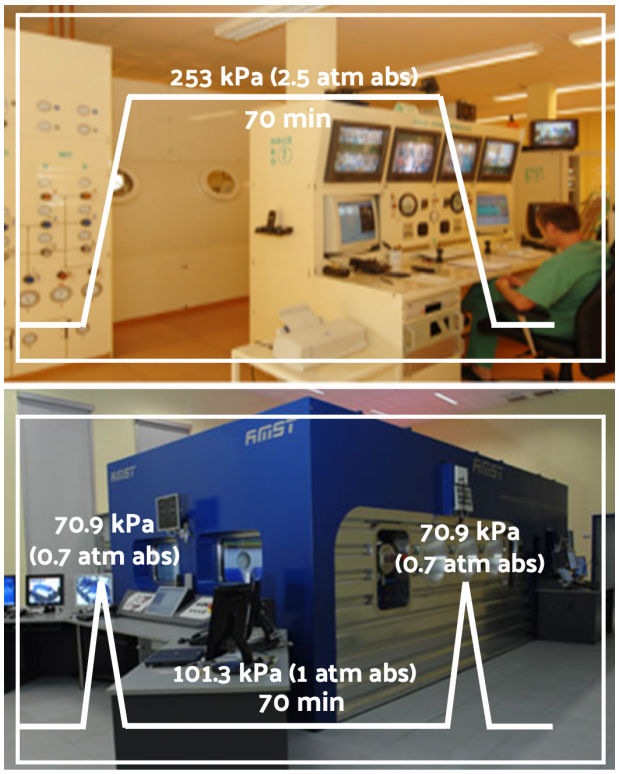
the Military Hospital in Brussels, Belgium, while patients in groups C and D were treated inside the hypobaric chamber of the Centre for Aerospace Medicine of the same hospital. Both treatment chambers are adjacent to the offices of the CHBO and all consultations, tests and evaluations were performed by the staff of the CHBO in the offices of the CHBO. Thus, the only variable in the treatment schedule was the actual treatment chamber. Actual pressure indications were blocked out in both treatment chambers. Patients in groups C and D were first decompressed to 10,000 feet altitude (70.9 kPa [0.7 atm abs])), then recompressed to ground level pressure, starting their treatment (either 100% or 21% oxygen) at the end of this decompression/compression period. Then, at the end of each treatment, the same decompression/compression was performed (Figure 1). This ensured that patients in all four groups had similar pressure-change related effects (notably, necessity of active or passive middle ear equalisation).

While the technical personnel responsible for administering the treatments obviously were not blinded to the gas breathed, the inside attendants were not aware of the oxygen pressure given. The attending physicians were instructed not to reveal the gas if required to attend to one of the patients in the study. The questionnaires and tests were administered by personnel unaware of the treatment group. Then, all the results were compiled in anonymised data sheets (MS Excel), and each group received a different group allocation letter (A, B, C, or D) by the principal investigator, who was not directly involved in the statistical analysis. The researchers performing the statistical analysis were thus equally unaware of the treatment groups they were analysing.

The 10 sessions were given daily over the course of two weeks, with a weekend break in between. During the week following completion of the 10 sessions, patients were again invited to a medical consultation, recording in a short questionnaire their subjective experience, as well as the occurrence of side effects and whether they were aware of the actual treatment modality. Also, we probed as to the subjective satisfaction of patients, asking them whether they would recommend their treatment to other Long COVID patients and whether they would be willing to pay for such a treatment, if required.

Then, the same questionnaires and tests were administered as before the start of the treatment. Quality of Life (QoL) symptoms were evaluated with a Visual Analogue Scale (VAS), the European quality of life 5-dimensions tool (EuroQoL EQ-5D-5L)[11] and the modified COVID-19 Yorkshire Rehabilitation Scale (C19-YRSm)[12] questionnaires. The VAS score evaluated the 'general quality of life', a score of 100 meaning 'feeling really great with no symptoms' and a score of 0 meaning 'feeling the worst I've ever felt'. The EQ-5D-5L and C19-YRSm scores measure specific symptoms and difficulties performing certain tasks and aspects of daily life, thus, a lower score on these scales indicates a better quality of life. EQ-5D-5L has a maximum score of 20 points, and C19-YRSm has a maximum score of 108 points. The subjective treatment effects were analysed as percents of the initial score, the initial score being considered '100'. For VAS, an 'after' score higher than 100 means improvement, for EQ-5D-5L and C19-YRSm, an 'after' score lower than 100 indicates improvement ('less difficulties').

Figure 1
Compression/decompression treatment profiles

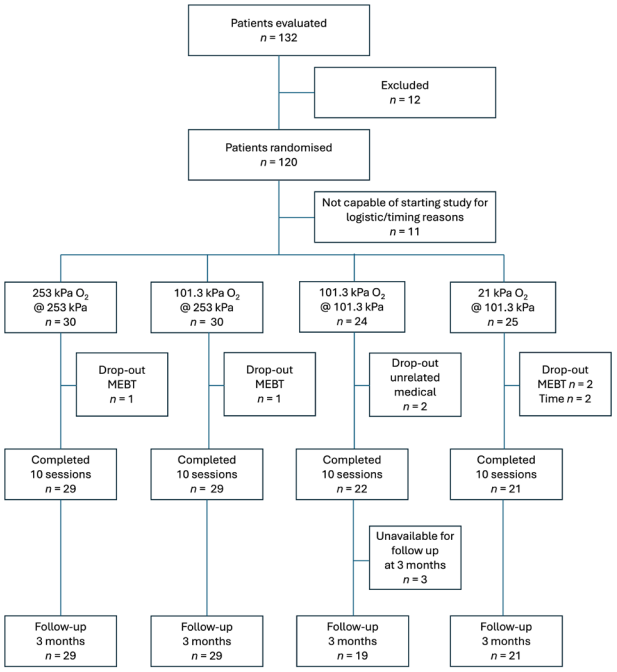


Physical condition was measured with a 6-Minute Walking Test (6MWT)[13] with peripheral oxygen saturation (SpO_2) measurement and the Borg Rating of Perceived Exertion (RPE) scale[14] before and after the test. The score was calculated as a percentage of normal performance (6MWD – 6-minute Walking Distance) for age and sex, according to the following formulae:[15]

Males: 6MWD = (7.57*body length [cm]) – (5.02*age) – (1.76*weight [kg]) – 309 m
Females: 6MWD = (2.11*body length [cm]) – (5.78* age) – (2.29* weight [kg]) + 667 m

Neurocognitive performance was evaluated with a computerised testing battery (Psychology Experiment Building Language, PEBL 4.1.9) using five different neurocognitive tests.[16] Short term memory was measured with Digit Span Backward (DSB) testing; speed of simple processing with Simple Reaction Time (REA); formal cognitive function with the Math Processing test (MathProc); hand-eye coordination with a Trail-making Test (PTrails) and spatial awareness with a Time Wall test (TimeWall).

Figure 2
Study flowchart. MEBT – middle ear barotrauma; Time – patient could not participate anymore because of time constraints



As there are no normal reference values available for each of these tests, individual results 'after' versus 'before' were calculated in percent, the initial results being considered '100'. For these scores, a score higher than 100 indicates improvement.

At three months post-treatment, a short telephone questionnaire probed for patient awareness of the study allocation, patient satisfaction and lasting effects.

Based on the single case series reporting on 10 patients[7] published prior to inception of the present study, we assumed an *a priori* effect size of 10% in the measured parameters, with a standard deviation of 5% in both groups; with an alpha error of 0.05 and a power of 0.90, requiring 18 subjects in each group (G*Power calculator 3.1 software, Heinrich Heine University, Düsseldorf, Germany).

Statistical analysis was performed on GraphPad Prism 10.0 for MacOS (GraphPad Software, Boston, MA).

Data are presented as mean (standard deviation [SD]). Normality of the data was verified by means of the Shapiro-Wilk test. Compared to baseline, data were analysed with a paired *t*-test for intragroup comparison. If gaussian distribution was not warranted, a Wilcoxon signed-rank test was preferred. Kruskal-Wallis or one-way analysis of variance (ANOVA) test with Bonferroni correction was used for intergroup multiple comparisons. Taking the baseline measures as '100', outcome measures were calculated as percents of the initial score for each exposure protocol, allowing an appreciation of the magnitude of change rather than the absolute values. Statistical significance was then assessed by means of a one-sample *t*-test.

Results

In total, 101 patients completed the study, of whom 98 were available for three months follow-up. After randomisation, 120 patients were scheduled to start, but 11 could not be included because of time constraints or logistic difficulties (unrelated to Long COVID). During the study period, four patients dropped out for medical reasons unrelated to Long COVID (two) or study logistics (two). Four patients dropped out because of middle ear barotrauma, two in the 2.5 ATA pressure groups (A and B) and two in the 101.3 kPa (1 atm abs) pressure groups (C and D). Three patients could not be contacted for the three month follow-up interview. Figure 2 shows the study flow diagram.

All groups were comparable with regards to demographics, previous history of burn-out, chronic 'psychophysical' illness (including fibromyalgia, chronic fatigue syndrome) or psychiatric disease, Long COVID duration, symptoms and severity (Table 1). All of the participants contracted COVID before the availability of SARS-CoV-2 vaccines, although most had been vaccinated when it became available.

After treatment, there was no significant difference in subjective symptoms (VAS), functional scores (EQ-5D-5L, C19-YRSm and 6MWT), and cognitive performance (PEBL) between the various treatment groups (Table 2). The response to treatment was highly variable, with some patients in even the 'most placebo' group D (21 kPa [0.21 atm] oxygen at 101.3 kPa [1 atm abs]) reporting a subjective improvement in their well-being. This resulted in some of the scores (marked in **bold** in Table 2) being significantly improved after the study treatment – however without a significant inter-group difference. We could not identify definite subgroups of patients responding better to any of the treatments. A more detailed analysis of the results of the C19-YRSm scores showed that patients with predominantly pulmonary symptoms seemed to have more improvement of these symptoms after a hyperbaric treatment at 253 kPa (2.5 atm abs); patients with systemic symptoms had an improvement with either 101.3 kPa (1 atm abs) or 253 kPa (2.5 atm abs) oxygen rather than 21 kPa (0.21 atm) oxygen; and that patients with predominant neurocognitive impairment (brain fog) apparently had fewer subjective complaints after treatments at 253 kPa (2.5 atm abs) (either 101.3 kPa or 253 kPa oxygen) (Table 3).

Side effects of the treatment were significant and mostly related to the confinement in a pressure chamber, wearing a mask. Middle ear barotrauma was rare, and equally distributed among the groups, and not substantially different from what has been reported in other HBOT studies. However, four patients had to stop the study because of middle ear barotrauma, two in each pressure condition. A

Table 1

Demographics and severity of Long COVID syndrome; *previous history of burn-out, psychiatric disease, chronic fatigue syndrome, fibromyalgia (see manuscript text); 6MWT – 6-minute walking test; C19-YRSm – modified COVID-19 Yorkshire Rehabilitation Scale; EQ-5D-5L – European quality of life 5-dimensions tool; ns – not significant ($P > 0.05$); QoL – quality of life; SD – standard deviation; VAS – visual analogue scale

Allocation	Group A	Group B	Group C	Group D	*P*-value
	253 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 101.3 kPa	21 kPa O_2 @ 101.3 kPa	
Age (years)	43.7 (SD 11.2)	49.4 (SD 10.3)	50.0 (SD 11.8)	46.8 (SD 8.2)	ns
Male sex	10/29 (34%)	15/29 (51%)	13/22 (58%)	13/21 (61%)	ns
Military personnel	10/29 (34%)	11/29 (37%)	8/22 (36%)	6/21 (29%)	ns
Long COVID (months)	21.46 (SD 9.34)	22.21 (SD 10.77)	21.67 (SD 9.49)	25.50 (13.44)	ns
Previous history*	6/29	4/29	3/22	3/21	ns
QoL VAS score	58/100	47/100	57/100	47/100	ns
EQ-5D-5L score	5/20	7/20	5/20	6/20	ns
C19-YRSm score	32/108	38/108	30/108	40/108	ns
Baseline 6MWT	87%	94%	96%	88%	ns
Disability from work	13/29 (45%)	14/29 (48%)	9/22 (41%)	10/21 (47%)	ns

Table 2

Change (percent of initial score) in quality of life scores and cognitive performance after treatment; baseline scores taken as 100; per-group values, one-sample Student *t*-test: $*P < 0.05$, $**P < 0.01$; § – multiple group comparison, Kruskal-Wallis test, right-most column, all non-significant (ns), $P > 0.05$; 6MWT – 6-minute walking test; C19-YRSm – modified COVID-19 Yorkshire Rehabilitation Scale; EQ-5D-5L – European quality of life 5-dimensions tool; DSB, REA, MathProc, Ptrails, TimeWall see Methods; ns – not significant ($P > 0.05$); PEBL – psychology experiment building language tests, see ref [16]; VAS – visual analogue scale; significant changes in bold (see Discussion for interpretation)

Allocation	Group A	Group B	Group C	Group D	*P*-value §
	253 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 101.3 kPa	21 kPa O_2 @ 101.3 kPa	
VAS	104.3	**81.67****	105.4	100.9	ns
EQ-5D-5L score	111.4	92.53	98.06	**80.87***	ns
C19-YRSm score	**67.42****	83.36	83.85	86.69	ns
6MWT	104.7	101.6	103.6	100.3	ns
PEBL – DSB	115.6	115.8	131.5	134.1	ns
PEBL – REA	96.51	105.3	100.7	101.1	ns
PEBL – MathProc	**109.2****	107.2	100.3	115.8	ns
PEBL – Ptrails	109.7	93.01	103.7	97.61	ns
PEBL – TimeWall	110.8	94.80	96.54	96.77	ns

significant logistical burden was reported: daily transport to the hyperbaric centre (some patients actually rented an apartment for the duration of the study), the fact that treatment consumed most of their daily time. Even if there were no direct costs involved for the participants, some may have spent significant amounts to organise their participation.

The telephone questionnaire at three months showed that none of the patients was aware of the actual treatment he/she had received. Patients from each group reported they felt the treatment had provided a 'real benefit', were glad to have participated and would be willing to pay for further treatment, if it were to be offered. However, most of the patients, even those who reported an improvement immediately after completion of the study period had returned to their pre-study condition when queried three months later, and only a small proportion of those not working at the start of the study had resumed a (part-time or full-time) professional activity. There was no significant difference in an inter-group analysis for any of these results (Table 4).

It is interesting to note that of the military patients, 30 of 35 (85.7%) were working at the start of the study, as opposed to 28 of 68 (41.2%) civilian patients. Military patients were

Table 3

Symptom improvement (number of points improved) as scored with C19-YRSm questionnaire, according to core symptom cluster (statistical significance not reached due to small numbers); figures marked in bold are discussed in the text; SD – standard deviation

Allocation	Group A	Group B	Group C	Group D	*P*-value
	253 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 101.3 kPa	21 kPa O_2 @ 101.3 kPa	
Pulmonary (max score = 24)	**4.16** (SD 0.69)	**4.27** (SD 0.71)	2.42 (SD 0.40)	2.17 (SD 0.36)	ns
Systemic (max score = 28)	**4.40** (SD 0.62)	**4.75** (SD 0.67)	**5.33** (SD 0.76)	2.50 (SD 0.36)	ns
Ear-Nose-Throat (max score = 8)	1.22 (SD 0.61)	2.60 (SD 1.30)	0.67 (SD 0.33)	1.75 (SD 0.87)	ns
Psychological (max score = 28)	5.25 (SD 3.30)	4.00 (SD 2.94)	4.00 (SD 2.82)	3.37 (SD 3.20)	ns
Neurological (max score = 20)	**3.08** (SD 0.61)	**4.63** (SD 0.92)	1.58 (SD 0.31)	2.06 (SD 0.41)	ns

Table 4

Questionnaire results (positive responses) after 3 months (scoring 0–5, scores > 3 counted as 'positive response'); multiple group comparison, Kruskal-Wallis test showed all changes non-significant, $P > 0.05$

Allocation	Group A	Group B	Group C	Group D
	253 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 253 kPa	101.3 kPa O_2 @ 101.3 kPa	21 kPa O_2 @ 101.3 kPa
Allocation concealment	29/29	29/29	22/22	21/21
'Felt a real improvement' after the treatment	20/29 (69%)	17/29 (59%)	9/22 (41%)	9/21 (43%)
'Happy to have participated'	25/29 (86%)	9/29 (31%)	17/22 (77%)	18/21 (86%)
'Would be willing to pay for further treatment'	22/29 (76%)	22/29 (76%)	10/22 (45%)	12/21 (57%)
Returned to professional activity at three months	4/29 (13%)	6/29 (20%)	2/22 (9%)	2/21 (9%)
Condition at three months similar compared to pre-study condition	18/29 (67%)	11/29 (38%)	13/22 (59%)	15/21 (71%)

also predominantly male (31 of 35, 88.6%), as opposed to civilian patients (21 of 68, 30.9% males).

Discussion

The evaluation of quality of life (QoL) and subjective well-being was performed with validated questionnaires, the more detailed one (C19-YRSm) having been specifically validated for Long COVID.[12] The 6MWT is a standardised, validated measure of physical exhaustion at exercise.[13] The PEBL neuro-psychometric testing battery evaluated specific domains shown to be affected by COVID infection, such as attention, processing speed, executive functioning, category fluency, memory encoding and recall.[17] Our evaluation battery of tests, both subjective and objective, was thus particularly adapted to the condition studied.

Even though some groups showed a significant effect on some scores and tests, there was no significant inter-group effect from different levels of oxygen breathing (21, 101.3 or 253 kPa [0.21, 1.0 or 2.5 atm]) in a pressure chamber. Our prospective, blinded, placebo-controlled study could thus not confirm the positive results of 10 sessions of HBOT (253 kPa oxygen), that previously published papers have reported. Neither was there any significant effect from breathing 101.3 kPa (1.0 atm) oxygen at either 101.3 or 253 kPa (1.0 or 2.5 atm abs) ambient pressure. Therefore, the null hypothesis (no combination would yield a better result than 21 kPa [0.21 atm] inspired oxygen at 101.3 kPa [1.0 atm abs] ambient pressure) cannot be rejected.

However, subjectively, in all groups a relatively high number of participants reported a positive effect of their treatment. This can only partially be explained by a detailed analysis of the predominant symptom cluster (Table 3). While it makes sense that pulmonary symptoms might be slightly more improved after a treatment at 253 kPa (there is a slight expiratory resistance of approximately 2–3 cm H_2O in the hyperbaric chamber breathing system, which might be equivalent to respiratory muscle training); while it may also make sense that breathing oxygen for 70 minutes per day could improve cognitive and systemic function slightly (hyperoxia has been shown to counteract inert gas narcosis effects[18–20] and, according to widespread belief, might

possibly improve cognitive function after alcohol use); this secondary analysis does not allow us to conclude that certain subgroups of patients would be better candidates for HBOT than others.

Other possible explanations for these subjective results may be the variability and fluctuation of Long COVID symptoms, and/or a placebo effect.

The symptoms and signs of Long COVID syndrome are highly variable and may be explained by many pathophysiological mechanisms.[6] No one single mechanism can explain all symptoms and signs, leading many to believe that Long COVID is an adverse (exaggerated) immune reaction targeting most, if not all, body systems and organs, albeit not all in an equal manner. Whether this immune reaction is caused by a continuous and excessive inflammatory response or to the continued presence of viral particles, is not known. In any case, the clinical course of Long COVID is fluctuating in time, with good periods alternating with exacerbations. There may be a gradual improvement over months or years, however, this may be difficult to appreciate because of the frequent relapses. This makes the evaluation of clinical efficacy of any treatment very difficult.

Patients become desperate because the medical world has no answer yet to their problem, and many feel that their symptoms are not well understood and/or minimised by their doctors, caregivers and (often also) their environment (work contacts, family). This desperation leads them to seek comfort in patient groups (such as on Facebook) where treatments are discussed and often recommended without there being any scientific proof (in essence, the personal experience of one or a few fellow sufferers makes them willing to also try these treatments).

In this regard, a remarkable similarity may be noted between Long COVID and other neuro-muscular syndromes, such as chronic fatigue syndrome and fibromyalgia.[21] While an organic cause, such as a chronic infection, is suspected to possibly be at the root of (some of) these syndromes, clear evidence that there is a causal relation is not yet available.[22] Long COVID, much like these other syndromes, may be susceptible to placebo response simply because the idea that 'someone takes their complaints and symptoms – finally – seriously' may already improve their general feeling of wellbeing. The three-case series,[7–9] published before we started our study (2021) and during our study period (2022 to mid 2023) were small (10, 12 and 59 patients respectively), uncontrolled, not blinded and evaluation was mainly subjective, and thus were highly likely to be subjected to placebo effects.

However, (even moderate) hyperoxia does play a role in inflammation and related processes, and thus, could exert an effect independent of pressure.

Oxygen plays a much greater role in our bodies than was previously appreciated. Not only a source of energy, oxygen serves as a signalling molecule and, while 'oxy-inflammation' certainly exists, oxygen at certain doses may have generalised anti-inflammatory effects, as can be determined in biochemical in-vivo studies such as performed by our own group.[23–26] Their clinical relevance, however, has not been determined. While providing extra oxygen to cells may seem a simple and easy way of modulating biochemical processes, the optimal dose of hyperoxygenation has yet to be defined. Low to moderate oxygen dose (30 to 142 kPa [0.30 to 1.4 atm]) administration has different effects than high-dose oxygen,[27,28] and the net effect seems to depend on the balance between oxidative effects and antioxidant counter-effects.[25] The optimal duration of repeat oxygen-mediated stimulation has been determined with reasonable success for certain conditions treated with HBOT. Some conditions require only 10 or less hyperbaric oxygen sessions, others would need 40 to 60 treatments for the clinical effect to reach a plateau. For conditions such as diabetic wounds or radiation cystitis, a clinical effect can usually be observed after 10 to 15 sessions. Which treatment duration would be necessary for a clinical effect in the case of Long COVID is not known. However, relying on biochemical changes alone to show a therapeutic effect is not ideal, as for many of the biochemical parameters that have been reported to change after oxygen stimulation, 'normal' values are not known or there may be a circadian or other fluctuation that is as yet unexplored.

The study treatments were chosen to allow for an evaluation of hyperoxygenation at two levels, 101.3 and 253 kPa (1.0 and 2.5 atm). The reasons behind this choice were threefold. First, it allowed to treat patients in mixed groups inside a single pressure chamber: the chambers are equipped with individually switchable breathing gas mixtures, and patients in the hyperbaric chamber were treated at our standard treatment pressure of 253 kPa (2.5 atm abs), either receiving 100% oxygen (for 253 kPa [2.5 atm] oxygen) or 40% oxygen (nitrox 40, for 101.3 kPa [1.0 atm] oxygen). In the other pressure chamber, the hypobaric chamber, patients were treated at 101.3 kPa (1.0 atm abs), breathing either 100% oxygen (for 101.3 kPa [1.0 atm] oxygen) or air (for 21 kPa [0.21 atm] oxygen). The second reason these oxygen pressures were chosen, is that – in case 101.3 kPa (1.0 atm) oxygen would be found to have a therapeutic effect and air not – this would open the path to a possible treatment with normobaric oxygen mixtures, which would obviously be easier to make available to many more patients without needing the logistics and costs of a hyperbaric treatment. Finally, by incorporating an 'intermediate' level of hyperoxia in our study protocol, this allowed us to design the protocol with an effective placebo for both 'high' and 'intermediate' hyperoxic treatments.

In both pressure chambers (in all study groups) there was, at the start and end of each treatment, a (de)pressurisation

phase during which active or passive ear equalisation manoeuvres were needed. Not surprisingly, middle ear barotrauma did occur in all groups, though seldom severe enough to warrant interruption of the study. However, this may have contributed to a placebo effect in all groups, which was intentional as the aim of the study was to verify only the therapeutic effect of hyperoxygenation, not the combined effects of oxygen and the 'hyperbaric treatment setting'. Therefore, the expectations of all patients and the 'ritual' surrounding the administration of the treatments needed to be as similar as possible.[29]

In addition to creating similar environments and subjective experience for all study groups, care was taken to ensure that no patient felt he or she was in a 'less valuable' group. It was explained that the different dosages of oxygen given, by their biological effect, or the breathing from a mask inside a pressure chamber, by a mechanical, respiratory training effect, could all lead to a beneficial therapeutic result. Furthermore, no patient was ever charged for any of the treatments or consultations, as this was a scientific study. Finally, all patients received the formal promise that, should one oxygen dosage or regimen prove to be significantly effective, they would be offered a new course of the 'most effective' treatment free of charge in our institution, the Military Hospital being a non-commercial medical institution.

Since our study started, the results of a prospective, randomised controlled trial (RCT), were published comparing a series of 40 HBOT sessions (100% oxygen, 203 kPa) with a series of 'placebo' treatments (breathing air at 104.4 kPa) in a hyperbaric chamber.[30] This paper, which is to date the only randomised controlled trial on HBOT for Long COVID,[31] reports a small but statistically significant improvement in certain neuro-psychometric domains, as well as changes in perfusion MRI imaging of the brain. While this study shows some morphological and functional changes in patients after 40 HBOT sessions, it is not at all clear whether this resulted in a significant and meaningful improvement in their clinical condition. Even though this study claims to be 'blinded and placebo-controlled', the possibility remains that the observed changes were induced by a placebo effect.

The high probability of placebo effects in HBOT has been discussed extensively before,[32,33] and has been considered an important factor in the proclaimed results of open-labelled studies (using either HBOT or so-called 'mild hyperbaric therapy'), cross-over studies or studies using as 'sham' a hyperbaric chamber compression to 132 kPa.[33,34] All these publications, based on which HBOT or 'mild hyperbaric therapy' has been advocated for chronic debilitating diseases (including chronic traumatic brain injury,[35,36] chronic fatigue syndrome,[37] cerebral palsy,[38] autism,[39] fibromyalgia,[40,41] chronic stroke[42] and post-traumatic stress disorder[43]) fail to take the possibility of placebo effect into account. In some of these studies, functional brain imaging (f-MRI, SPECT) is used to objectively demonstrate a change after hyperbaric therapy. However, it has been shown that placebo effects, notably those induced by a positive expectation, can induce observable changes in brain metabolism almost to the same level as 'true' treatment.[29] Patients are willing to pay a sometimes-hefty price for hyperbaric oxygen treatments – which is often cited as proof 'that the treatment must be effective'. However, placebo effect may also play a significant role here; it has been experimentally shown that the price of an ineffective treatment increases the perceived effect, as well as the willingness to administer more doses of the expensive drug.[44] Recently, it was shown that placebo treatment, if causing some physical discomfort to the patient, also increases the placebo's 'perceived action' in comparison to an identical, but fully inert placebo, even inducing changes in cerebral fMRI images.[45]

In the Zilbermann study,[30] the 'control' condition consisted of a compression to only 122 kPa (1.2 atm abs) followed by gradual decompression to 104.4 kPa (1.03 atm abs). While the 'ritual' and 'expectations of improvement' may have been similar in both groups, it seems unlikely that significant middle ear discomfort was present in control patients. In most cases, significant middle ear discomfort and barotrauma only shows after a pressure gradient of more than 30 kPa (0.3 atm).[46,47] This could very well explain the larger proportion of patients responding to 'true' hyperbaric oxygen treatment. Therefore, the results reported in this study should be interpreted with caution.

Conclusions

Our prospective, randomised, placebo-controlled study did not show a significant effect from different levels of oxygen breathing (21, 101.3, or 253 kPa [0.21, 1 or 2.5 atm]) in a pressure chamber. The positive results from 10 sessions of HBOT at 253 kPa (2.5 atm) oxygen, as reported in previous studies are not confirmed in our study. Although our treatment course was shorter than the 40 sessions recently published, our results suggest that the overall very modest clinical improvements reported in that study may very well have been due to a placebo effect.

Because of the potentially high logistic burden and financial cost of HBOT and the 'false hope' that such a treatment may give, the claims that HBOT has a significant effect on Long COVID need to be further verified before indiscriminately prescribing or promoting HBOT.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Belgian Defence Military Hospital servers. The full study protocol and all questionnaires are available upon simple request.

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