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Research article

Methodology and Preliminary Observations on Hypoxic–Hyperoxic Therapy Using the CellOxy System in Healthy Volunteers: A Single-Arm Pilot Study

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Abstract: Intermittent hypoxic–hyperoxic exposure therapy (IHHT) has become a promising approach in adaptive training that may stimulate mitochondrial biogenesis, improve redox homeostasis, and enhance cardiopulmonary efficiency. However, standardized clinical protocols and safety validation in healthy populations are still insufficient. Objective: This prospective pilot study assessed the feasibility, safety, and physiological tolerance of the IHHT using the CellOxy intelligent system in healthy volunteers. The study was conducted at the Teaching Emergency Hospital "Bagdasar-Arseni" (SCUBA), with approval from the institution's Bioethics Committee. Healthy adult volunteers underwent structured IHHT consisting of 4 cycles of hypoxia [Fraction of Inspired Oxygen (FiO2) 9–16%, titrated in order to reach a target oxygen saturation (SpO2) ~ 85%], alternating with 3–4 cycles of hyperoxia (FiO2 33–37%), each hypoxic cycle lasting 4 minutes and each hyperoxic phase 2 minutes; one session lasted approximately 30 minutes. Sessions were repeated 2–3 times per week for one month. Cardiopulmonary exercise testing (CPET) and complete blood count (CBC) analyses were performed at baseline and after the intervention. All participants completed the intervention without any adverse events. Preliminary data indicate improved exercise tolerance and stable hematological parameters, consistent with good physiological adaptability. The CellOxy-based IHHT protocol was safe and well-tolerated in healthy volunteers. This adjunctive therapy may be applicable in neuro- and cardiopulmonary rehabilitation. Further controlled studies with extended biomarker assessment are necessary.

Keywords: Intermittent Hypoxic–Hyperoxic Therapy, IHHT, oxygen therapy, mitochondrial adaptation, aerobic capacity, cardiopulmonary performance

1. Introduction

In recent decades, IHHT has attracted increasing scientific interest due to its potential to promote neuroplasticity and enhance adaptive mechanisms in both the central and peripheral nervous systems. Controlled hypoxia triggers the body's adaptive defenses, increasing systemic resilience by enhancing erythropoietin production and improving redox balance. One of the pathophysiological mechanisms by which it acts is the stabilization of hypoxia-inducible factor-1α (HIF-1α), which initiates transcriptional cascades that increase the formation of new blood vessels (angiogenesis), glucose metabolism, and mitochondrial biogenesis. Subsequently, when the therapy

switches to hyperoxia, oxidative phosphorylation increases and reactive oxygen species (ROS) detoxification accelerates, along with adenosine triphosphate (ATP) production [1–7].

Both hypoxic and hyperoxic stimuli combined induce a hormetic response balancing oxidative stress, thus improving systemic resilience. Such biphasic oxygen therapy has been associated with favorable outcomes in patients with cardiovascular, neurodegenerative, pulmonary, and musculoskeletal disorders, as well as in those with chronic fatigue syndromes. Its multisystem effects-improving pulmonary diffusion capacity, oxygen transport, and mitochondrial oxygen utilization-make IHHT a versatile therapeutic tool [8-10].

IHHT is underpinned by a biological rationale emanating from both preclinical and clinical evidence. Brief periods of hypoxia also stimulate angiogenic signaling and capillary growth in skeletal muscle, increase glycolytic efficiency, and enhance muscular endurance. Kon and colleagues showed that resistance training under hypoxic conditions increases the expression of vascular endothelial growth factor (VEGF) and increases the capillary-to-fiber ratio, while also improving muscle endurance, in addition to normoxic training alone. This emphasizes the importance of hypoxia as one of the key modulators of muscle plasticity. In conjunction with standard rehabilitation modalities - physiotherapy, neuromuscular electrical stimulation, neurocognitive rehabilitation and therapeutic exercise - IHHT training has been found to optimize functional outcomes in adults with various ailments, especially in disorders characterized by disturbed neuroenergetic balance [6,10,11-13].

In the real world, clinically, the applications of IHHT range widely from aging populations and cardiovascular disorders to weight-management programs and stress-related conditions such as burnout. It also attracts interest in basic research, including immune modulation and host responses in infectious diseases, including Coronavirus Disease 2019 (COVID-19), where hypoxia at admission was a predictive factor for worse outcomes. Indeed, researchers from the field of sports science and adaptive physiology are investigating the possibility that controlled oxygen oscillations can enhance performance and accelerate recovery in challenging environments [13-17].

Advances in technology offer intelligent oxygen-delivery platforms that can monitor physiological parameters in real-time while automatically adjusting FiO_2. Such a device is CellOxy, which is among a new generation of IHHT equipment that combines adaptive oxygen modulation with SpO_2-based feedback and safety cut-offs to maintain personalized exposure ranges with minimal operator input. These intelligent systems overcome some disadvantages of older IHHT devices, which often relied on fixed FiO_2 levels and offered little control over individual variability in responses to desaturation. For example, with CellOxy, this automatic control enhances the reproducibility of the protocols and minimizes risks of overly deep hypoxia; this is a particularly relevant consideration when designing future clinical applications in more vulnerable neurological or cardiometabolic-at-risk populations [12].

Preliminary pilot studies on similar smart IHHT platforms report improvements in aerobic capacity, cognitive function, autonomic regulation, and metabolic biomarkers, supporting the translational potential of such technologies [9,18,19].

Still, there is significant inter-individual variability, and standard exposure parameters are not yet established. Despite encouraging mechanisms and pilot data from small trials, large gaps persist in standards for IHHT protocols, safety profiles, dose–response effects, and inter-individual variation in healthy adults. Many reports vary considerably in FiO_2 ranges, exposure durations, and monitoring methods, making comparability and clinical integration problematic [2,8,20]. Thus, defining normative tolerance patterns and the physiological limits of the so-called “safe hypoxic–hyperoxic dose” in healthy individuals is a very important step toward extending IHHT to populations at higher risk, such as post-stroke patients, individuals who

suffered a traumatic brain injury (TBI), or elderly subjects with diminished cardiopulmonary reserve.

Given the aforementioned clinical gap, this pilot study's objectives were to test the feasibility, tolerability, safety, and preliminary physiological responses to a standardized IHHT protocol delivered via the CellOxy intelligent device in a group of healthy adult volunteers. Another aim is to generate preliminary evidence for future clinical trials in neurorehabilitation, cardiopulmonary and metabolic conditioning, and personalized oxygen-based therapies by detailing baseline response profiles and confirming the feasibility of automated FiO_2 modulation.

2. Materials and Methods

2.1 Study Design and Ethical Approval

This was a single-arm prospective pilot study conducted at the Neuromuscular Rehabilitation Clinic of SCUBA in Bucharest. This study obtained ethical approval from the Institutional Bioethics Committee (approval no. 44367/19.09.2024). This study also complied with all the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent from all study subjects to use their medical records for research, including in accordance with the General Data Protection Regulation (GDPR), was obtained before study enrollment.

2.2 Eligibility criteria

Recruited volunteers included healthy adults (20–50 years) with no acute cardiopulmonary, hematological, respiratory, or neurological disorders, anemia, or pregnancy. Each volunteer underwent a preliminary clinical examination, including a resting electrocardiogram (ECG) and baseline SpO_2 assessment to confirm suitability for IHHT exposure.

Demographic and clinical characteristics, including age, sex, current smoking status, body mass index (BMI), and baseline functional parameters such as the resting heart rate and maximal oxygen uptake (VO_2 max), were recorded. As a brief related parenthesis, VO_2 max is a measure of cardiopulmonary aerobic fitness, measured by the peak volume of oxygen the body can utilize for intense exercise.

2.3 Device Description: CellOxy Intelligent IHHT System

IHHT sessions were performed by using a CellOxy® intelligent oxygen-modulation system. This consisted of:

- Automation of FiO_2 control, with an accuracy of about 1% for both hypoxic and hyperoxic values;
- Safety algorithms, integrated to prevent excessive desaturation;
- Automatic calibration at startup;
- Use of an individual, sealed full-face mask for each participant.

Each participant had their own mask; thus, no intermediate disinfection of devices was needed.

2.4 Patient Registration and Pre-Session Preparation

A personalized profile was set up during the first visit within the CellOxy interface, using name, date of birth, height, weight, smoking status, and current medication.

Before every session:

- participant was placed in the supine position;
- the individual pulse oximeter and mask were fitted;
- blood pressure was measured pre- and post-session to ensure safety;
- ECG monitoring was performed for participants with cardiovascular risk;
- Participants were asked not to speak, nor move around unnecessarily, and to keep relaxed for clear signal stability and accurate adjustment of FiO_2.

2.5 Hypoxic Testing and Individualization of FiO_2

Prior to initiation of therapy, all subjects underwent two standardized tests of hypoxia. These tests allowed the calibration of individual optimal values of FiO_2 for hypoxic conditions and perfecting of the SpO_2 algorithm that controlled oxygen delivery.

2.6 IHHT Intervention protocol

All sessions utilized the intelligent hypoxia–hyperoxia program. Each IHHT session consisted of:

- Hypoxic phase: FiO_2 10–12%, duration 4-6 min with target SpO_2 ~ 80–88%;
- Hyperoxia phase: FiO_2 30–40%, duration 2-3 minutes;
- Number of cycles: 4-7 hypoxia–hyperoxia cycles/session;
- Total duration: 30-40 minutes/session;
- Frequency: 2-4 sessions/week for a total of 8-12 sessions / four-week program.

The CellOxy device adjusted FiO_2 proportionally according to the measured SpO_2 in order to maintain exposure within a person's individual physiological range. All experiments were performed with constant supervision by members of the same clinical team in a temperature- and humidity-controlled room.

2.7 Monitoring and Safety Criteria

As outlined above, vital parameters were monitored throughout all sessions.
Therapy was discontinued in the event of the following:

- SpO_2 < 80%;
- angina-like symptoms;
- sustained arrhythmias;
- dyspnoea;
- symptoms suggestive of ischemia;

Perceived exertion and any subjective discomfort were also recorded.

2.8 Outcome Measurements

The participants were assessed at pre- and post-intervention on:

- CPET-to evaluate the degree of endurance, VO_2 max, and cardiovascular adaptation.
- CBC-to monitor hematological responses and detect possible erythropoietic or oxidative effects.
- Monitoring of vital signs: SpO_2 and heart rate at the beginning and end of each session for cardiopulmonary and hemodynamic stability.

Additional observational data: perceived exertion, subjective discomfort, and symptoms during hypoxia/hyperoxia phases.

Figure 1 below exemplifies a flowchart of the study, showing the chronological process of recruiting participants, taking baseline measurements, conducting intervention sessions with IHHT, and post-intervention measurements.

Figure 1. Overview of the study workflow and evaluation timeline.

Figure 2 illustrates an example of a cyclical pattern of SpO_2 and heart rate values in a single IHHT procedure. This graph depicts the characteristic saturation-resaturation wave, accompanied by a sharp physiological rebound, during hyperoxic phases, underlining the precision and the repeatability of the exposure protocol.

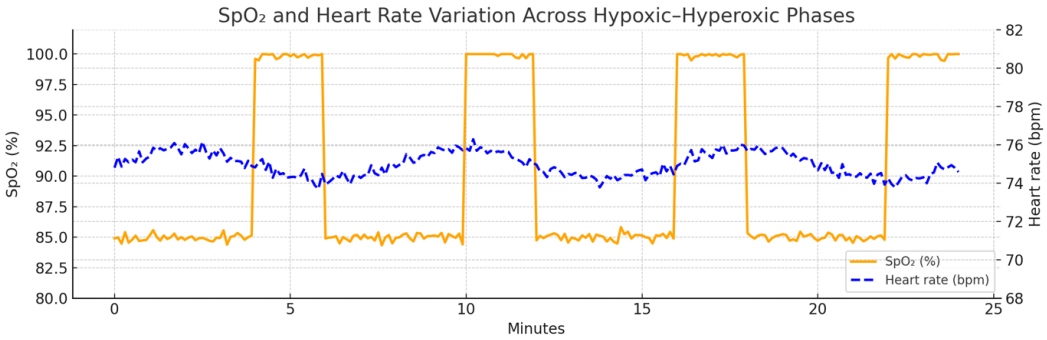

Figure 2. Example of cyclic oxygen saturation and heart rate variation during an IHHT session.

2.9 Data Analysis

The initial dataset was created in Microsoft Excel 2010, and all subsequent statistical analyses were conducted in International Business Machines Corporation Statistical Package for the Social Sciences, version 29 (IBM SPSS Statistics for Windows, Version 29.0.2.0) [16]. For the continuous variables, the results are presented as mean ± standard deviation (SD). Comparisons for pre- and post-intervention were made using paired t-tests, where distributional assumptions were satisfied or non-parametric equivalents otherwise. The predefined level of statistical significance was $p < 0.05$ at a 95% confidence interval (CI). Given the heterogeneity in participant ages, Pearson correlation coefficients were also calculated to examine the possible relations of age with baseline physiological variables and age with longitudinal changes (Δ) that occurred across the one-month follow-up. Delta values were calculated as the arithmetic difference between post- and pre-intervention measures (Δ = post - pre) to quantify the individual-level hemodynamic and cardiopulmonary changes. These correlation analyses are exploratory because of the small sample size.

3. Results

This pilot study included 20 healthy volunteers. Regarding demographic characteristics, sex distribution was nearly equal, with 11 females and 9 males. These participants were aged between 25 and 44 years, with a mean age of 34.6 ± 7.8 years, indicating a diverse age distribution within the specified range (Figure 3). Seven patients reported that they smoke regularly. On average, the subjects had a normal BMI of 19.49 ± 4.79 kg/m^2. Throughout the intervention, all volunteers attended each session and reported no adverse symptoms (no dizziness, presyncope, chest pain, dyspnea beyond expected physiological responses, or any other symptom that required clinical intervention), and blood pressure and heart rate remained in safe ranges, highlighting the safety and tolerability of the procedures.

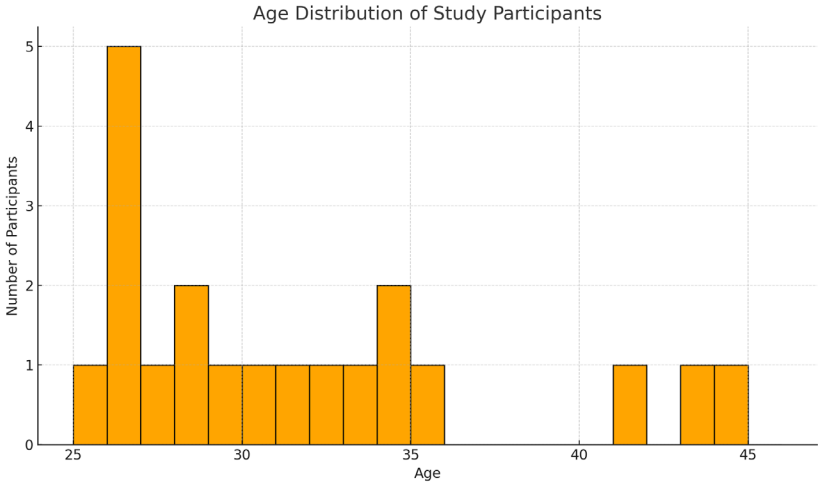

Figure 3 – Age distribution of the healthy volunteers included in the study

Although the study enrolled 20 healthy volunteers, only seven participants had completed the full IHHT program and reached the one-month follow-up at the time of this preliminary analysis, due to ongoing enrollment over the past 4 months. For these individuals, complete paired measurements of hematological and cardiopulmonary variables were available. Follow-up of the remaining participants is ongoing, and additional paired datasets will be included in the extended analysis planned for the next phase of the study.

The seven participants included 3 females and 4 males, with a mean age of 31.85 ± 7.9 years. Three participants reported their current smoking status. The average BMI was 24.48 ± 5.08 kg/m², falling within the normal to slightly overweight range.

After the 4-week IHHT intervention, there was no change in the hematological parameters - no significant differences were observed between baseline and post-intervention values for red blood cell count (RBC), hemoglobin (HGB), or hematocrit (HCT) - indicating the absence of short-term hematopoietic stimulation or dilutional effects. Mean RBC values were 4.88 ± 0.46 mil/μL at baseline and 4.79 ± 0.33 mil/μL post-intervention, while HGB remained practically unchanged (14.63 ± 1.28 g/dL vs. 14.56 ± 1.01 g/dL). HCT also demonstrated comparable values (43.36 ± 3.45% vs. 42.06 ± 2.84%).

On the other hand, the exercise parameters displayed heterogeneous responses. The peak workload achieved during CPET did not change significantly following the IHHT program: 176.29 ± 49.14 W before versus 173.00 ± 54.46 W after the intervention ($p = 0.400$). In contrast, there was a modest but statistically significant reduction in VO_2 values after the intervention: 29.80 ± 3.80 mL/min/kg versus 26.60 ± 1.54 mL/min/kg, $p = 0.046$, suggesting a possible adaptive enhancement in cardiopulmonary performance (refer to Table 1 and Figures 4 and 5 for details).

Variable, Mean ± SD	Before IHHT	After IHHT	p-value
RBC (mil/μL)	4.88 ± 0.46	4.79 ± 0.33	0.498
HGB (g/dL)	14.63 ± 1.28	14.56 ± 1.01	0.718
HCT (%)	43.36 ± 3.45	42.06 ± 2.84	0.199
VO_2 (mL/min/kg)	29.80 ± 3.80	26.60 ± 1.54	**0.046***
Workload (W)	176.29 ± 49.14	173.00 ± 54.46	0.4

Table 1. The results of the paired t-test for the variables of interest before and after the clinical intervention

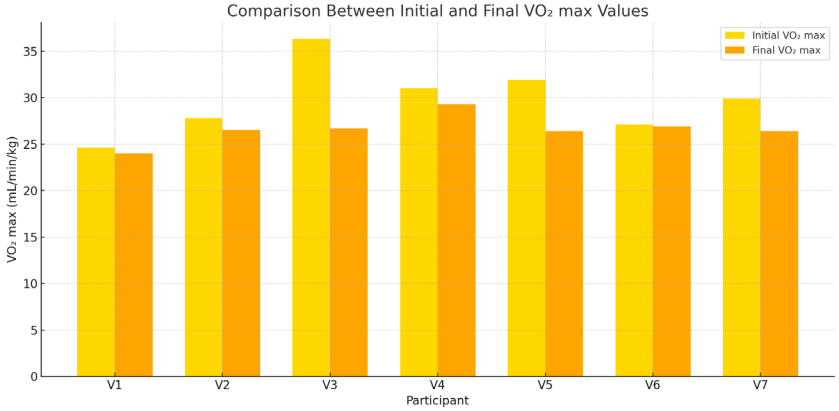

Figure 4. A graphical comparison between the initial and the last VO_2 max values among study participants

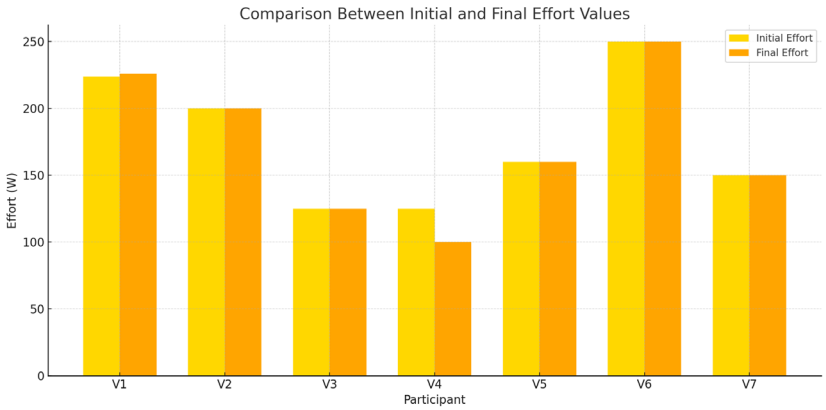

Figure 5. A graphical comparison of the initial and final peak workload during CPET

Additionally, subjective tolerance was excellent: none of the participants reported dizziness, dyspnea, or discomfort severe enough to interrupt sessions. Transient desaturation (SpO_2 ~ 85%) during hypoxic cycles was well tolerated, with rapid normalization during hyperoxia.

Recovery kinetics during hyperoxia were fast and uniform across participants, indicating good physiological adaptability to cyclic oxygen fluctuations.

Given the participants' age range, we used Pearson correlation analysis to determine whether age was associated with baseline physiological metrics or with changes in these parameters after the intervention. Age was inversely related to baseline hemoglobin ($r = –0.77$, $p = 0.045$) and hematocrit ($r = –0.82$, $p = 0.025$), suggesting lower erythroid indices in older subjects. Although the cohort had a relatively narrow age range (25–44 years), this pattern is consistent with previously described mild age-related declines in erythroid parameters among healthy adults. There were no significant associations between age and baseline VO_2 or maximal workload.

With respect to longitudinal changes, age significantly correlated with ΔHGB ($r = 0.78$, $p = 0.037$), while no other significant association was observed for ΔRBC, ΔHCT, ΔVO2, or ΔWorkload. These findings suggest that age did not substantially affect the cardiopulmonary response to IHHT. These observations should be interpreted as exploratory, given the small group size.

Variable	Baseline	Baseline	Δ	Δ
	r	**p**	**r**	**p**
RBC (mil/μL)	–0.73	0.06	0.52	0.23
HGB (g/dL)	–0.77	**0.045**	0.78	**0.037**
HCT (%)	–0.82	**0.025**	0.49	0.26
VO_2 (mL/min/kg)	0.1	0.83	–0.27	0.56
Workload (W)	–0.18	0.7	–0.06	0.89

Table 2. *Results of the Pearson correlation coefficients (r) between age and variables of interest; Δ = change from baseline to follow-up; bold indicates p < 0.05.*

In addition, BMI was inversely associated with baseline VO_2 (r = -0.86, p = 0.013), indicating that higher BMI was associated with lower aerobic capacity. In contrast, BMI was also positively associated with baseline peak workload (r = 0.89, p = 0.0067). Concerning longitudinal changes, there were no significant associations between BMI and changes in VO_2, workload, or hematological variables for either condition.

Variable	Baseline	Baseline	Δ	Δ
	r	**p**	**r**	**p**
RBC (mil/μL)	0.05	0.91	0.44	0.32
HGB (g/dL)	0.32	0.48	0.3	0.52
HCT (%)	0.11	0.82	0.57	0.18
VO_2 (mL/min/kg)	**–0.86**	**0.013**	0.65	0.11
Workload (W)	**0.89**	**0.0067**	0.42	0.34

Table 3. Results of the Pearson correlation coefficients (r) between BMI and variables of interest; Δ = change from baseline to follow-up; bold indicates p < 0.05.

4. Discussion

This pilot study reports preliminary data suggesting that IHHT using the CellOxy intelligent system is safe, feasible, and well-tolerated among healthy subjects. The periodic cycles of both hypoxia and hyperoxia elicited physiological responses without inducing hematological imbalance or adverse effects. The small but statistically significant improvement in VO_2 max also indicated that IHHT could effectively improve aerobic fitness.

These results are in congruence with existing literature that has already shown the capability of controlled oxygen cycles for inducing mitochondrial biogenesis, increasing oxidative phosphorylation, or optimizing redox homeostasis. The strategy employed within the current study seems to avoid severe hypoxia and can stimulate a mild hormetic response for increasing cardio-pulmonary resilience and manageable adverse events [14,22].

Correlation analysis showed that age and BMI contributed to inter-individual differences in baseline physiological parameters, but had minimal impact on changes caused by the IHHT intervention. The negative associations between age and baseline hemoglobin and hematocrit align with previously reported mild age-related hematological changes in healthy adults [23-25]. However, the narrow age range of 25 to 44 years limits the physiological interpretation of these findings.

BMI indicated strong associations with baseline VO_2 and workload, suggesting that body composition may influence cardiopulmonary performance. These findings are physiologically plausible as individuals with higher BMI may exhibit lower mass-specific oxygen consumption and higher workloads. Notably, BMI did not correlate

with ΔVO_2, ΔWorkload, or hematological shifts, suggesting that body mass did not modulate the short-term response to IHHT.

Even if the current findings are promising, they should be interpreted with caution due to the small sample size and the absence of a control group. Nonetheless, this study offers a valuable methodological basis for the design of standardized IHHT protocols.

IHHT's safety profile, which was documented among healthy participants, also supports its potential integration among the current neurorehabilitation protocols targeting diseases that involve compromised mitochondrial activity, neuroinflammation, stroke, brain injury, and neurodegenerative diseases [16,17,20,26]. Given its pathophysiological mechanisms, this treatment may help patients adapt better to intensive neurorehabilitation and complement other treatments for optimal results [6,10,11,19].

The absence of negative events in the group aligns with the so-called therapeutic window of hormesis, in which intermittent mild hypoxia elicits adaptive rather than stress responses. Besides, the characteristic dynamics of desaturation and resaturation during therapy reflect the flexibility necessary for successful IHHT treatment [14,22].

In addition to the benefits seen for aerobic systems, the biological processes underlying the effects of IHHT, such as HIF-1α stabilization, angiogenesis, mitochondrial biogenesis, and mitochondrial 'economization', reflect processes shown in controlled experimental studies. It is essential to note that studies on acute intermittent hypoxia have shown serotonin-mediated long-term facilitation, BDNF signaling, and excitability of the motor pathways, mechanisms that are immediately relevant for the recovery of motor function following stroke, spinal cord injuries, TBI, and neurodegenerative diseases [1-5,27].

Moreover, IHHT is suitable for implementation within contemporary digital healthcare systems. Smart FiO_2 control, together with continued physiological observation, provided by the CellOxy system, facilitates personalized oxygen supply, and the safe and automated adjustment of therapy makes it suitable for the possible implementation of IHHT within the framework of data-based rehabilitation processes, supervised by healthcare professionals [1,2].

Our study results offer a needed baseline for healthy subjects that is essential for the safe implementation of IHHT in the presence of stroke, brain injury, neurodegenerative, pulmonary, or cardiovascular diseases.

Study Limitations

The main limitation of the current study is its small sample size and the absence of a control group. This restricts the generalizability of findings. Biochemical parameters of oxidative stress and inflammation were not evaluated. Nonetheless, the present results provide a robust basis for future randomized clinical trials, an endeavor we are pursuing.

5. Conclusions

This pilot study demonstrates that IHHT treatment via the CellOxy intelligent system is safe, well-tolerated, and effective in inducing measurable physiological effects. The effects of short-term IHHT exposure brought about a consistent enhancement of aerobic capacity, without adverse hematological or cardiovascular effects, thus confirming the feasibility of the experimental procedure and the beneficial adaptive response to well-controlled hypoxia.

Future studies need, accordingly, to:
• quantify the biochemical, metabolic, inflammatory, and neurophysiological biomarkers of IHHT-induced adaptation, related to angiogenesis, mitochondria, and neuroplasticity.
• investigating IHHT for use as a preparatory or adjunct therapy for neurorehabilitation, especially with neurologic disorders that affect oxidative metabolism or neuroplasticity;
• examining dose-response relationships and long-term effects with controlled randomized studies, since the specific role of dosing in determining beneficial versus maladaptive effects in hypoxia-based treatments cannot be overlooked.
• integration of IHHT with artificial intelligence-based monitoring systems, feedback systems using sensors, and digital twins for rehabilitation to enhance the efficiency of individual response profiling.
Taken together, these results place IHHT on the shortlist of promising, non-invasive physiological conditioning modalities with high translational potential. When performed via sophisticated, feedback-guided systems like CellOxy, IHHT potentially offers a new, valuable tool for the improvement of cardiometabolic function, neuroplasticity, and personalized rehabilitation.

Abbreviations

ATP - adenosine triphosphate
BMI - body mass index
CBC **-** complete blood count
CI – confidence interval
COVID-19 - Coronavirus Disease 2019
CPET- Cardiopulmonary exercise testing
ECG - electrocardiogram
FiO_2 - Fraction of Inspired Oxygen
GDPR - General Data Protection Regulation
HCT - hematocrit
HGB - hemoglobin
HIF-1α - hypoxia-inducible factor-1α
IBM SPSS - International Business Machines Corporation Statistical Package for the Social Sciences
IHHT - Intermittent hypoxic–hyperoxic exposure therapy
RBC - red blood cell count
ROS - reactive oxygen species
SCUBA - Teaching Emergency Hospital "Bagdasar-Arseni"
SpO_2 - oxygen saturation
TBI - traumatic brain injury
VEGF - vascular endothelial growth factor
VO_2 max - Maximal Oxygen Uptake

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