

IMPACT OF INTERMITTENT HYPOXIA-HYPEROXIA THERAPY IN COPD PATIENTS - PILOT STUDY

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ABSTRACT

Introduction. Intermittent hypoxia-hyperoxia therapy can contribute to increasing exercise tolerance in patients with cardiovascular, bronchopulmonary, metabolic, and neuropsychiatric pathologies, according to studies in the specialized literature. This therapy consists of the use of hypoxic intervals, interspersed with hyperoxic episodes.

Material and methods. We present 7 clinical cases of patients admitted to the Balneal and Rehabilitation Sanatorium of Techirghiol (SBRT) for 2 weeks, complaining of polyarticular mechanical pain. These patients were diagnosed with chronic obstructive pulmonary disease (COPD) by the pulmonologist according to the GOLD criteria. During hospitalization, the patients underwent a complex balneo-physical-kinetic treatment, simultaneously with intermittent hypoxia-hyperoxia therapy. Patients were evaluated both at admission and discharge.

Results. The evolution of the patients was favorable, with improvement in symptoms, spirometry, scales used, 6-minute walk test, HTi index and paraclinical investigations. Improvements were identified in respiratory volumes, but also in total serum cholesterol and blood glucose levels.

Conclusions. Obtaining promising results gives indications that intermittent hypoxia-hyperoxia therapy can be an alternative treatment for multiple pathologies, including COPD. The therapy proved to be safe and well tolerated, representing a non-pharmacological therapy that can be included in the therapeutic management of patients with COPD.

Keywords: intermittent hypoxia-hyperoxia, COPD.

Introduction

COPD represents a major health problem globally, causing a significant increase in social and economic burden through its impact on morbidity and mortality (1). In 2012, COPD was responsible for three million deaths, which represents 6% of all deaths globally (1).

The pharmacological therapy for COPD is complex, involving the use of a wide range of medications. Respiratory rehabilitation is an essential component of the therapeutic approach, aiming to reduce dyspnea, improve general health, increase exercise capacity, reduce

hospitalizations, and improve symptoms of anxiety and depression (1).

Intermittent hypoxic training (IHT) is a non-invasive and easily applicable technique that involves repeated exposure to a mixture of low-oxygen gases interspersed with normoxic periods (2). There is significant variation in IHT protocols concerning cycle duration, number of hypoxic sessions, and frequency of training days (3).

IHT has been used in the field of sports medicine as a potentially beneficial strategy to improve exercise performance in athletes and has also been considered in healthy subjects as a

possible way to improve physiological functions (4).

Numerous studies in the literature conducted over the years have demonstrated the beneficial effects of IHT, including improved exercise tolerance in patients with cardiovascular, respiratory, and metabolic syndrome, improved cardiometabolic status in elderly patients, and increased cognitive potential in Alzheimer's disease (5).

Intermittent hypoxia-hyperoxia training (IHHT) has been integrated into medical practice as a training method that uses periods of increased oxygen concentrations (hyperoxia) instead of normoxia, between hypoxic breathing sessions. During these sessions, the patient receives a gas mixture containing between 30% and 40% O₂ (6).

Intermittent hypoxia-hyperoxia sessions can be implemented in two main ways: with patients at rest, called IHHE (intermittent hypoxic hyperoxic exposure), or during physical exercise - IHHT (intermittent hypoxic hyperoxic training) (7).

Material and methods

In this study, we present 7 clinical cases of patients admitted to SBRT for 2 weeks. The initial group consisted of 12 patients, but 2 suffered a hypertensive crisis, one presented anxiety when using the device mask, and two requested discharge for personal reasons. These patients were diagnosed with COPD according to the GOLD criteria. They were in a stable respiratory condition, following pharmacological treatment as recommended by the pulmonologist.

All subjects signed the Informed Consent form to participate in the study. The study began after obtaining approval from the SBRT Ethics Committee, number 13945/01.09.2023.

During the hospitalization, the participants performed complex balneo-physical-kinetic treatment, concomitant with intermittent hypoxia-hyperoxia therapy generated by a control unit. Both at admission and discharge, the patients were evaluated as follows: spirometry, 6-minute walk test, HTi index, blood samples were collected, Functional Independence Scale (FIM), Visual Analogue Scale (VAS), assessment

scale for the risk of falling, the depression scale, the anxiety scale and a test assessing the impact of symptoms on patients' lives.

The complex balneo-physical-kinetic rehabilitation treatment that the patients received included: hydrokinetotherapy, hydrothermotherapy, electrotherapy, massotherapy, kinetotherapy, but also intermittent hypoxia-hyperoxia therapy. IHHT was applied according to the prescribed protocols, once daily.

The inclusion criteria were as follows: a positive diagnosis of COPD according to GOLD criteria; patients in a stable phase of the disease; patients willing to sign informed consent after being explained the purpose and treatment they would undergo; patients receiving optimal pharmacological treatment for associated pathologies.

The exclusion criteria were the following: refusal to sign the informed consent; lack of confirmation of COPD diagnosis; intolerance to hypoxia; infusions with vitamin C or administration of high doses of vitamin C (orally over 1000 mg/day) or administration of beta-blockers; decompensated pathologies; patients with contraindications for the complex balneo-physical-kinetic treatment.

Results

Table 1. Demographic characteristics of the patients in the study.

		Patients	
		Count	%
Total		7	
Gender	Feminin	6	85.7%
	Masculin	1	14.3%
Residence	Urban	3	42.85%
	Rural	4	57.15%
Educational level	Gymnasium	2	28.5%
	High school	5	71.5%
	Faculty	0	0%
Professional status	Employed	1	14.3%
	Unemployed	0	0%
	Retired	6	85.7%
Age	50-60	1	14.3%
	60-70	3	42.85%
	>70	3	42.85%

The demographic data of the patients in the study were detailed in the following table and included data about patients such as gender,

residency, education level, professional status, and age (Table 1).

Analyzing the patients' data, it was found that the majority were women (85.7%). Regarding the residence, most of the patients lived in rural areas (57.15%). 5 patients had graduated from high school (71.5%) and none of the participants had higher education. More than 85% of the patients were retired, with only one being employed at the time of the study (14.3%). Regarding the age of the patients, the average age was found to be 66.14 years.

Table 2 VAS Scale. FIM Scale. Assessment scale for the risk of falling.

		Patients	
		Count	%
Total		7	
VAS Scale	Improved score	5	71.5%
	Unimproved score	2	28.5%
FIM Scale	Mild functional deficit	7	100%
	Medium functional deficit	0	0%
	Severe functional deficit	0	0%
Assessment scale for the risk of falling	Minimal risk	5	71.5%
	Moderate risk	2	28.5%
	High risk	0	0%

A percentage of 71.5% registered a significant improvement in the value of the VAS scale at discharge. All 7 patients were classified in the "Mild Functional Deficit" category. 5 patients (71.5%) fit into the "Minimal risk" category, indicating a low risk of falling during hospitalization. The data indicate that 2 patients are classified as having a "Moderate Risk", but no patient falls into the "High Risk" category.

A percentage of 28.5% (2 patients) are exposed to at least one environmental factor. 14.2% (1 patient) is exposed in the workplace. 28.57% (2 patients) are currently smokers. 42.85% (5 patients) were non-smokers at the time of evaluation. 28.57% (2 patients) are former smokers who have quit. 57.15% of the patients are currently undergoing pharmacological treatment for COPD, while 42.85% of the patients are not receiving pharmacological treatment.

The data indicate that a significant number of patients (85.7%) experienced a significant improvement in their depression score. At

discharge, 4 patients showed a state of normal depression, moving from a high level to a lower one, which suggests a significant improvement. Regarding the anxiety scale, out of a total of 7 patients, 6 of them showed an improvement in their anxiety score, representing 85.7%. Six out of 7 patients, accounting for 85.7%, demonstrated an improvement in the anxiety scale category, moving from higher levels of anxiety to lower levels of anxiety.

Table 3 Exposure to environmental factors. Professional exposure. Smoking. Treatment.

		Count	%
Patients		Total	7
Exposure to environmental factors	Yes	2	28.5%
	No	5	71.5%
Professional exposure	Yes	1	14.2%
	No	6	85.8%
Smoking	Yes	2	28.57%
	No	3	42.85%
	Former smoker	2	28.57%
Treatment for COPD	Yes	4	57.15%
	No	3	42.85%

Table 4 Scale for depression. Scale for anxiety.

	Results	Count	%
Scale for depression-Score	Improved score	6	85.7%
	Unimproved score	1	14.3%
Scale for depression-Scale category	Progression	4	57.14%
	Stagnation	2	28.57%
	Regression	1	14.28%
Scale for anxiety-Score	Improved score	6	85.7%
	Unimproved score	1	14.3%
Scale for anxiety-Scale category	Progression	6	85.7%
	Regression	1	14.3%

In all cases, the 6-minute walk test showed improvement compared to the time of admission. Test - the influence of symptoms on patient's lives was improved at discharge in 6 patients (85.7%), with only one patient (14.3%) showing no notable changes. The Tiffeneau index was improved at discharge in 5 patients (71.4%).

Table 5 6-minute walk test. Test - symptoms on patients' lives. Tiffeneau index.

	Results	Count	%
6-minute walk test	Improved score	7	100%
	Unimproved score	0	0%
Test- the influence of symptoms on patients' lives	Improved score	6	85.7%
	Unimproved score	1	14.3%
Tiffeneau index	Improved score	5	71.4%
	Unimproved score	2	28.6 %

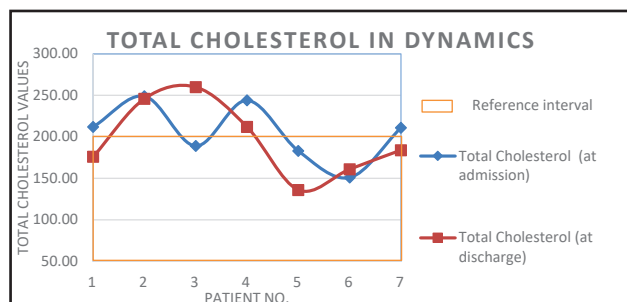


Figure 1. Total cholesterol in dynamics.

A significant percentage, 71.5% of the total patients (5 out of 7), recorded a substantial improvement in their total cholesterol levels at discharge.

The results indicate an improvement in blood glucose levels for 6 patients (85.7%), while one patient (14.3%) had the same blood glucose value at discharge, representing a stagnant value.

In the case of the HTi (Hypoxic Training Index), a percentage of 100% indicates that all 7 patients showed improvement at discharge, following the completion of treatment.

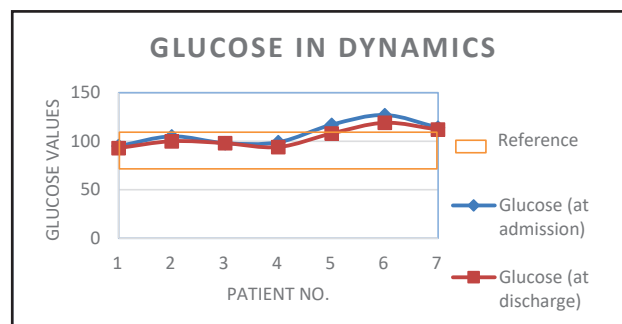


Figure 2. Glucose in dynamics.

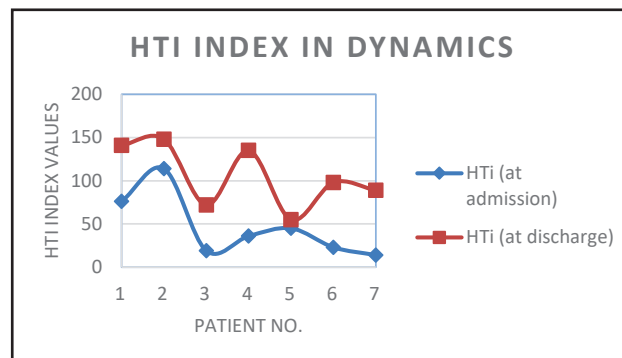


Figure 3. HTI index in dynamics.

Discussions

The limitations of the study were as follows: a small number of patients were included in the study; although COPD is a common pathology, many patients admitted to SBRT were long-term smokers or had professional exposure to a toxic environment and did not have a positive diagnosis of COPD according to GOLD criteria;

Table 6. Paraclinical investigations.

Analyzed parameter – Reference value	Time of assessment	Pat. no 1	Pat. no 2	Pat. no 3	Pat no 4	Pat. no 5	Pat. no 6	Pat. no 7
Urea (10.0-50.0 mg/dl)	A	44.5	30.4	34.3	32.8	46.8	29.1	46.7
	D	39.3	34.7	37.4	36.8	64.7	29.3	37.2
Uric acid (F: 2,6—6; B: 3,5-7,2 mg/dl)	A	4.75	4.65	3.56	4.1	3.74	4.18	5.73
	D	4.35	4.91	4.29	4.49	6.81	3.96	4.77
Creatinine (F: 0,6—1,1; B: 0,9-1,3 mg/dl)	A	1.22	1.19	0.85	0.92	1.47	1.09	1.25
	D	1.23	1.29	1.02	0.88	1.77	1.13	1.19
Glucose (70-105 mg/dl)	A	95	105	98	99	117	127	114
	D	93	100	98	94	108	119	112
Total cholesterol (<200 mg/dl)	A	212	249	189	244	183	151	211
	D	176	246	260	212	136	161	184
AST (<40 U/L)	A	23	26	21	25	42	42	19
	D	22	15	22	31	55	36	19
ALT (< 41 U/L)	A	16	16	14	28	50	74	15
	D	25	14	16	41	60	86	20

A= admission

D= discharge

the intervention period may probably be too short. Nevertheless, this study allowed us to demonstrate that IHHT concurrently with balneophysical-kinetic treatment, can bring significant improvements, even within a relatively short intervention period.

From the analysis of the study cohort, it was observed that the majority of participants were women, residing in rural areas. Rural areas can have better or worse air quality, which may have a significant impact on COPD patients. This distribution may provide clues regarding the environmental influence on pulmonary health.

Regarding the level of education, more than 70% of the study patients had completed high school, indicating that even though they didn't have university or postgraduate degrees, they still paid special attention to health-related issues.

From the specialized literature, we learn that known risk factors for COPD exacerbations include tobacco exposure, certain workplace exposures, and bacterial and viral infections. Another potential trigger for such exacerbations is short-term exposure to air pollution (8). From the data presented, 2 patients were exposed to the environmental factors, and one patient was exposed at the workplace. This data can be used to assess health risks and implement appropriate protective measures for these patients. Although smoking is recognized as the most significant causal factor of COPD (9), in the study group, at the time of evaluation, there was a significant number of non-smokers (42.85%), and 28.57% (2 patients) were former smokers.

At the time of examination, 3 patients were not receiving medication for COPD. This suggests that in cases of mild COPD, medication may not be necessary. Ten studies were found that investigated non-pharmacological treatment, leading to a significant and clinically relevant improvement in health-related quality of life (HRQoL) compared to usual care or no treatment (10).

Regarding the depression scale category (0-7: normal depression; 8-17: mild depression; 18-25: moderate depression; over 25: severe depression), more than half of the patients (57.14%) showed a significant improvement in their depression status, moving from mild

depression to normal depression. This suggests that these patients experienced an improvement in their depressive symptoms.

The improvement in the anxiety score (85.7%) and the anxiety scale category (85.7%) reflects a positive progression in the patient's condition and may have a significant impact on their lives.

The 100% improvement in the 6-minute walk test can be highly encouraging and may suggest that intermittent hypoxia-hyperoxia therapy applied during hospitalization was effective and led to an increase in the exercise capacity of the studied patients.

The COPD assessment test is a new scoring system for COPD patients, providing a simple method for evaluating the impact of COPD on a patient's health (11).

The better discharge score regarding symptomatology (85.7%) suggests that the treatment was effective. The 71.4% score for the Tiffeneau index indicates that the majority of patients showed an improvement in lung function, which may indicate the treatment's effectiveness in enhancing pulmonary health.

Intermittent hypoxia-hyperoxia therapy had a significant impact on the serum total cholesterol levels in 5 out of 7 patients who showed an improvement at discharge. This observation suggests that the therapy can be an important factor in improving the cardiovascular health of these patients, as already demonstrated in the specialized literature (12,13,14).

The improvement in blood glucose levels at discharge in 6 out of 7 patients (85.7%) suggests that intermittent hypoxia-hyperoxia therapy may have a significant impact on blood glucose control. Glazachev's study from 2017 demonstrated that blood glucose was significantly lower at one-month follow-up after intermittent hypoxia-hyperoxia therapy (12). Clinical research indicates that there is a common occurrence of disturbed glucose metabolism, often manifesting as increased blood glucose levels, even when grade 1 obesity is not specifically mentioned (15).

The HTI index objectively quantifies the dose of hypoxia, providing a more objective measure of the hypoxic stress released during the IHT session (16). It was improved by 100%, thus

suggesting that intermittent hypoxia-hyperoxia therapy was effective and that the therapeutic goals were successfully achieved.

Conclusions

Analyzing the data from our study, it was found that intermittent hypoxia-hyperoxia therapy was well tolerated by all patients, and no adverse reactions were reported. Literature data confirm that exposure to this therapy can lead to beneficial outcomes for multiple pathologies.

This innovative non-pharmacological treatment approach, simultaneously with balneo-physical-kinetic treatment, can contribute to maximizing therapeutic benefits in the whole body. This therapeutic strategy, which includes both forms of treatment, may represent a promising alternative in the management of COPD patients.

Intermittent hypoxia-hyperoxia, applied either passively or in combination with physical exercise, seems to be a useful strategy for various pathologies, as demonstrated by studies in the specialized literature in recent years (17).

Although these results are promising, further research is expected to explore the benefits of intermittent hypoxia-hyperoxia therapy on larger patient populations and for other pathologies. IHHT has proven to be a safe and effective therapy in the patients included in the study, representing a non-pharmacological, well-tolerated therapy. It is hypothesized that this therapy could be integrated into the therapeutic management of various pathologies, including patients with COPD (18).

Declaration of conflict of interests.

No conflict of interest exists for any of the authors regarding this paper.

Informed consent.

This study was conducted by the declaration of Helsinki and with approval from the Ethics Committee of Balneal and Rehabilitation Sanatorium of Techirghiol from Romania. Written informed consent was obtained from the

patient.

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