HYPOXIC CONDITIONING IN POSTSTROKE REHABILITATION: AIMING TO IMPROVE EXERCISE TOLERANCE (PILOT STUDY)

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ABSTRACT

Background. Rehabilitation of stroke patients is a complex issue requiring a multidisciplinary approach using innovative physical and medicinal support. One such promising method is hypoxic conditioning (HC). Several studies have demonstrated its effectiveness in improving cardiorespiratory endurance, cognitive function, and emotional status in patients with chronic cardiovascular diseases and pulmonary pathology. However, this method has not been used in the rehabilitation of post-stroke patients.

Aim: To evaluate the efficacy and safety of HC treatments inclusion in particular protocols of intermittent hypoxic-hyperoxic exposures (IHHE), into a comprehensive rehabilitation program with the aim of enhancing exercise tolerance and cardiorespiratory efficiency in patients ≥6 months after ACCF.

Materials and methods. A prospective randomized controlled trial was conducted involving 23 patients who had suffered an ischaemic or haemorrhagic stroke ≥6 months earlier, divided into a study group (n=11) and a control group (n=12). The study group received standard rehabilitation with the addition of 10-12 IHHE procedures (FiO_2 0.11-0.12 hypoxic phase, FiO_2 0.35-0.40 hyperoxic phase). The control group received only the standard rehabilitation program. Outcomes were assessed based on the 6-minute walk test (6MWT), work performed (W, work-KJ), Borg scale, pre- and post 6MWT HR, blood pressure, haemoglobin saturation (SpO_2), as well as psycho-emotional state assessed before and after 3-weeks rehabilitation program.

Results. After the treatment, the study group demonstrated a 40.1% increase in the 6MWT distance (275.13 ± 60.34 m against 198.08 ± 80.34 m in the control group, $p<0.001$) and an 18.9% increase in the amount of work done (48.03 ± 12.45 vs. 38.09 ± 9.45 W, $p <0.01$). Subjective fatigue on the Borg scale decreased by 2.62 points in the study group ($p<0.05$); meanwhile, intergroup post-intervention differences levelled out ($p>0.05$). In the control group, the indicators changed insignificantly. HR, BP, and saturation indicators remained stable ($p > 0.05$).

Conclusion. Inclusion of IHHE in the standard rehabilitation program enhances the exercise tolerance and performance in patients after ACCF and it could be recommended for inclusion in comprehensive rehabilitation programs.
Keywords: intermittent hypoxic–hyperoxic exposure; hypoxic conditioning; stroke rehabilitation; exercise tolerance; post-stroke recovery; physical performance

Novelty Statement

This study explores the role of intermittent hypoxic–hyperoxic exposure (IHHE) as an adjunct to standard rehabilitation in patients more than six months after acute cerebral circulation failure (stroke), with a specific focus on restoring exercise tolerance. By prioritizing objective measures of exercise performance and endurance, it addresses an under-studied aspect of post-stroke recovery. The ongoing findings suggest that hypoxic conditioning may support adaptive responses relevant to physical rehabilitation and justify further controlled studies to clarify its optimal use and long-term value within multidisciplinary rehabilitation programs.

INTRODUCTION

Acute cerebral circulation failure (ACCF), or stroke remains one of the leading causes of disability and mortality worldwide. Approximately 15 million people suffer a stroke each year, 5 million of whom die, and 5 million more are left with permanent disabilities [1, 2]. Rehabilitation after a stroke is a complex, multi-component task, especially in the long term, when conventional rehabilitation methods often prove to be insufficiently effective [3, 4].

Among the key consequences of ACCF is a decrease in exercise tolerance (ET), which significantly limits patients' daily activities and impairs their quality of life [4,5]. A decrease in ET is associated with a complex of factors, including muscle weakness, impaired neuromuscular control, cardiorespiratory desadaptation, and psychological disorders such as depression and astenia [6]. Conventional rehabilitation methods, including therapeutic exercise, aerobic training, and physical therapy, are often insufficiently effective in patients with severe residual effects after stroke [7]. These limitations are due to both the objective constraints of the patients themselves (advanced age, comorbidity, cognitive impairment) and insufficient activation of neuroplastic and adaptive mechanisms under standard therapy [8].

Recent years have seen increasing attention directed towards methods capable of potentiating recovery processes through the activation of endogenous defense mechanisms. One such method is hypoxic conditioning (HC), specifically intermittent hypoxic-hyperoxic exposure

(IHHE) [9, 10]. This approach is based on the dosage-controlled exposure (breathing through the facial mask) to hypoxic and hyperoxic gas mixtures, which leads to the activation of key transcription factors such as HIF-1α (hypoxia-inducible factor) and Nrf2 (nuclear factor 2 associated with erythroid factor 2), which regulate the expression of genes responsible for angiogenesis, antioxidant protection, energy metabolism, and neuroplasticity [11, 12].

Experimental and clinical studies demonstrate that IHHE promotes improved cerebral perfusion, enhanced mitochondrial function, reduced oxidative stress and inflammation, and stimulation of neurogenesis and synaptogenesis [13-15]. An important aspect is the effect of HC on the cardiorespiratory system: it has been shown that HC procedures increase exercise tolerance, improve hypoxia tolerance, and optimize autonomic regulation of heart rhythm. These effects are particularly relevant for patients after ACCF, who often have comorbid cardiovascular diseases and reduced adaptive reserves [16, 17].

Although there's growing interest in using HC in neurorehabilitation, questions about its effectiveness and safety in restoring ET in stroke patients haven't been studied enough. Most existing work focuses on cognitive and motor functions, while the impact on physical endurance and tolerance to exercise needs more research. In addition, it is necessary to optimize IHHE protocols, taking into account individual patient characteristics such as age, duration of disease, baseline level of hypoxic resistance, and comorbidities.

Objective: To evaluate the efficacy and safety of inclusion of HC procedures, in particular intermittent hypoxic–hyperoxic exposures, into a comprehensive rehabilitation program with the aim of enhancing exercise tolerance in patients ≥6 months after ACCF.

MATERIALS AND METHODS

Research design

A prospective randomised controlled trial was conducted at N.V. Sklifosovsky Institute of Clinical Medicine, Sechenov University and Clinical Hospital No.1 JSC ‘Medsi Group of Companies’

Eligibility criteria

The study included patients: who had suffered an ischaemic or haemorrhagic stroke (6+ months ago); aged 45 years or older; with residual motor and/or cognitive impairments; who had signed an informed consent form.

Exclusion criteria: Acute mental disorders; acute infectious diseases; chronic somatic diseases in the acute and/or decompensated stage; presence of neoplastic processes; general contraindications to physiotherapy; general contraindications to therapeutic physical training.

Exclusion criteria: sharp deterioration in the patient's general somatic condition; oncological diseases; patient refusal to participate in the study.

Description of the research

Research participants (n=23) were randomised into two groups: the study group (n=11) and the control group (n=12). In accordance with the protocol of Clinical Hospital No. 1 of Medsi Group, all patients received a standard rehabilitation program adapted to their individual indications. In the main group, a course of IHHE was added to this program.

In the main group, patients underwent 10–12 IHHE procedures using the ReOxy® apparatus (3–5 times a week, 40 minutes each treatment). The session protocol provided for alternating hypoxic (FiO_2 0.11–0.12) and hyperoxic (FiO_2 0.35–0.40) phases in an intermittent exposure mode; during the procedures, continuous monitoring of haemoglobin saturation (SpO_2) and heart rate (HR). The apparatus is registered in the Russian Federation as a respiratory therapy device (registration certificate No. RZN 2014/1486 dated 30 April 2019).

The control group received only standard rehabilitation treatment with no IHHE.

Methods of recording outcomes

Before and after rehabilitation, all patients had a comprehensive assessment of their functional status.

exercise tolerance was measured using the six-minute walk test (6MWT), which objectively assesses the distance a patient can walk in a fixed amount of time. In addition, performance indicators (W, work-KJ), subjective exercise intensity on the Borg scale, as well as parameters of the body's physiological response to exercise, oxygen saturation (SpO_2) and heart rate (HR) were assessed.

Additionally, the psycho-emotional state was assessed using the DASS-21 questionnaire (Depression Anxiety Stress Scales), the level of fatigue using the MFI-20 (Multidimensional Fatigue Inventory), quality of life using the SF-12 questionnaire (Short Form-12 Health Survey) (results of psychic and emotional states dynamic are not presented in the current paper). A hypoxic test was used preliminary for each patient to assess individual hypoxic resistance and select proper IHHE treatments structure accordingly.

An individual registration card (observation log) was kept for each patient, where personal data and the results of the examinations were recorded.

Ethical expertise

The scientific research work was approved by the local ethics committee of I.M. Sechenov First Moscow State Medical University (Sechenov University) (extract from protocol No. 28-24 dated 21 November 2024). All study participants signed informed consent forms in accordance with the ethical principles set forth in the Declaration of Helsinki.

Statistical analysis

Data analysis was performed using descriptive statistics with calculation of the mean (M) and standard deviation (SD), presented as M±SD. Student's t-test was used to compare groups, and analysis of variance (ANOVA) was applied to evaluate the dynamics of indicators. The level of statistical significance of differences was taken to be $p < 0.05$. For multiple comparisons, the Bonferroni correction methodology was applied.

Research study duration

Recruitment of patients and the research study commenced in November 2024 and is scheduled to be completed in May 2026.

RESULTS

Research subjects (participants)

The research study included 23 patients (16 with ischaemic stroke and 7 with haemorrhagic stroke), with an average age of 63.2 ± 12.1 years. The main demographic and clinical characteristics are presented in Table 1.

Table 1. Clinical and demographic characteristics of patients

Variable	Study group	Control group	p-value
Age (years), M ± SD	62.33 ± 11.29	64.08 ± 15.21	0.721
Gender, n (%)	**n = 11**	**n = 12**	**0.714**
Male (M)	6 (42.9%)	8 (57.1%)	
Female (F)	5 (55.6%)	4 (44.4%)	
Length of illness (months.), M ± SD	28.00 ± 21.07	34.09 ± 24.36	0.482
BMI (kg/m²), M ± SD	27.11 ± 5.69	27.91 ± 4.12	0.655
Type of stroke, n			**0.627**
Ischemic	7 (3M/4F)	9 (6M/3F)	
Haemorrhagic	4 (3M/1F)	3 (2M/1F)	
Comorbidities, n			
Arterial hypertension	9 (6M/3F)	10 (7M/3F)	1
Diabetes mellitus	2 (1M/1F)	3 (3M/0F)	1
Coronary heart disease	3 (3M/0F)	7 (5M/2F)	0.243
Atrial fibrillation	1 (1M/0F)	5 (4M/1F)	0.174
Obesity	6 (4M/2F)	5 (3M/2F)	0.714
Medications administered			
Antihypertensive	10 (6M/4F)	10 (7M/3F)	1
Antidiabetic	2 (1M/1F)	3 (3M/0F)	1
Diuretics	5 (3M/2F)	7 (4M/3F)	0.714
Hypolipidemic	8 (5M/3F)	9 (7M/2F)	1
Anticoagulants	6 (4M/2F)	5 (5M/0F)	0.684
Antiplatelet	7 (5M/2F)	4 (2M/2F)	0.408
Proton pump inhibitors	5 (4M/1F)	7 (5M/2F)	0.684

Note: M ± SD - mean ± standard deviation; n - number of patients. For categorical variables, the p-value was calculated using Fisher's exact test; for quantitative variables, it was calculated using Student's t-test (assuming normal distribution).

Age: The groups are comparable ($p > 0.05$, t-test). Duration of disease: The control group has a longer duration of disease (but high variability). Body weight: No differences ($p > 0.05$).

Based on the data in Table 2, all patients in both groups got the standard rehab program from Clinical Hospital No.1 of Medsi Group, adjusted for individual needs; the main group also got IHHE training. A review of the treatment plan showed that most patients in both groups got key types of rehabilitation, like therapeutic physical exercises, massage, and physical therapy. Statistical analysis using Fisher's exact test did not reveal any significant differences in the frequency of use of any rehabilitation methods between the groups (p> 0.05 for all comparisons), which confirms the comparability of the groups in terms of the standard treatment received.

Table 2. Primary rehabilitation programs administered during recovery from ACCF

Variable	Study group	Control group	p-value
Therapeutic physical exercises	11 (6m/5f)	12 (8m/4f)	1
Theravital	6 (4m/2f)	5 (4m/1f)	1
Stabiloplatform (Huber-360)	5 (2m/3f)	5 (2m/3f)	1
Biological feedback training (C-Mill)	5 (3m/2f)	7 (5m/2f)	0.704
Robotic therapy (ARMEO)	7 (5m/2f)	5 (4m/1f)	0.704
Massage	10 (5m/5f)	12 (8m/4f)	0.723
Balneotherapy	7 (4m/3f)	8 (6m/2f)	1
Electrostimulation	7 (3m/4f	3 (2m/1f)	0.264
Laser therapy	8 (3m/5f)	8 (6m/2f)	0.684
Electromagnetic therapy	8 (5m/3f)	8 (6m/2f)	1

Note: Data are presented as n (number of patients) with distribution by gender (m/f); Fisher's exact test was used for comparison.

The homogeneity of the groups in terms of the standard therapy received made it possible to exclude its influence as a confounding factor and interpret the subsequent differences in efficacy in the context of adding a course of IHHE to the main group.

Evaluation of the effectiveness of intervention on physical exercise tolerance indicators

Statistical analysis of data using analysis of variance (ANOVA) demonstrated a significant positive trend in key indicators of physiological performance in the main group as compared to the control group. The baseline levels of external work performed (W) and 6MWT distance between the groups were statistically comparable (p>0.05), as shown in Table 3. After the intervention, a significant increase in work performed was recorded in the main group by 18.97% ($p < 0.01$), while in the control group the increase was statistically insignificant ($p > 0.05$). Group-to-group analysis confirmed that the increase in the W index in the main group was significantly higher ($p < 0.05$).

An identical but more pronounced trend was observed for the objective endurance index, the 6-MWT: in the main group, a highly significant increase in distance of 40.12% ($p < 0.001$) was recorded, which significantly exceeded the weak but significant increase in the control group of 12.24% ($p < 0.05$). Intergroup differences in 6-MWT dynamics were highly significant ($p < 0.01$)..

Table 3. Exercise Tolerance Indicators Before and After Intervention, with Post-Hoc Intergroup Comparisons (Bonferroni-corrected)

Variable	Study Group (M ± σ)		Control Group (M ± σ)		Post-Intervention Intergroup Comparison (Bonferroni correction)	
	Before	After	Before	After	p-value (α = 0.0167)	Significance
External work (W, kJ)	40.37 ± 11.24	48.03 ± 12.45	36.15 ± 8.52	38.09 ± 9.45	0.01	Significant
6-MWT (meters)	196.38 ± 50.21	275.13 ± 60.34	176.47 ± 70.21	198.08 ± 80.34	0.008	Significant
Borg scale (fatigue)	6.50 ± 1.07	3.88 ± 1.64	5.08 ± 2.39	3.25 ± 1.82	0.04	Insignificant

*Note: M – arithmetic mean, σ – standard deviation. Bonferroni correction applied for three pairwise comparisons (adjusted $\alpha = 0.05 / 3 = 0.0167$).

Subjective perception of exertion, assessed by the Borg scale, decreased significantly in both groups ($p < 0.01$), fully eliminating any initial differences. No significant intergroup differences were found in hemodynamic parameters (heart rate, systolic/diastolic blood pressure) or oxygen saturation (SaO_2) dynamics ($p > 0.05$ for all).

After Bonferroni correction, statistically significant intergroup differences persisted for objective performance indicators, external work (W, $p = 0.01$) and 6-MWT distance ($p = 0.008$), confirming reliable superiority of the intervention in the study group. The initial baseline difference in Borg scale scores ($p = 0.04$) lost significance after correction ($p > 0.0167$), indicating comparable starting levels and ruling out bias from initial fatigue perception.

The application of rigorous statistical evaluation criteria demonstrated that the main group exhibited more pronounced and reliable improvements in objective indicators of physical performance and endurance compared to the control group, highlighting the effectiveness of adding the IHHE program as a supplementary rehabilitation method following a stroke.

DISCUSSION

Study results demonstrate that adding an IHHE course to the rehabilitation program for patients after a stroke can lead to statistically significant and clinically relevant improvements in tolerance to exercise and physical performance.

The main criterion in the study was the distance covered in the 6MWT: the increase in the main group was 78.75 m (40.12%), which is more than three times higher than the control group (21.61 m; 12.24%) and significantly exceeds the minimum clinically significant difference (30–50 m). These results are consistent with recent studies showing that HC enhances recovery after stroke by increasing endurance and functional capacity [10,13,15,18].

The mechanism of improvement is possibly related to the activation of HIF-1α, which stimulates erythropoiesis, angiogenesis, and tissue metabolism, as well as enhances antioxidant defense and mitochondrial function [19-21]. Findings from mechanistic studies confirm that IHHE may promote neuroplasticity and cognitive recovery, which is particularly important for post-stroke patients [22,23]. The observed increase in physical performance in the main group may therefore relate not only to cardiorespiratory adaptation, but also to improved neural regulation of movement.

Subjective perception of exercise intensity on the Borg scale also demonstrated significant improvement: fatigue levels decreased, which increases motivation and commitment to rehabilitation. In addition, IHHE showed a good safety profile: the only side effects reported were short-term drowsiness and temporal dyspnea, which are consistent with data on the tolerability of similar protocols in geriatric and cardiological studies [24,25].

The effect of IHHE in this study significantly exceeded the effect of standard rehabilitation in the control group, highlighting the potential of the method as an additional non-pharmacological intervention. However, several publications indicate variability in patient’s response to hypoxic therapy, which requires an individualized approach to the selection of exposure regimens [18,21,24].

CONCLUSION

This study presents a prospective evaluation of hypoxic conditioning, specifically intermittent hypoxic–hyperoxic exposure (IHHE), as an adjunct to standard long-term stroke rehabilitation with a primary focus on restoring exercise tolerance. Unlike most existing research that emphasizes motor or cognitive recovery, this work specifically addresses exercise tolerance and functional endurance in patients more than six months after acute cerebral circulatory failure.

Adding IHHE to the rehabilitation program for patients after ACCF results in a significant improvement in exercise tolerance, performance capacity, and subjective perception of fatigue. The method is well tolerated and can be recommended for widespread implementation as part of multidisciplinary rehabilitation programs.

By integrating objective performance measures with physiological and subjective assessments, the study contributes new evidence on the potential adaptive benefits and safety of IHHE in this patient population. The ongoing findings support the rationale for considering hypoxic conditioning as a complementary component of multidisciplinary rehabilitation programs and provide a basis for further large-scale, controlled studies aimed at optimizing protocols and defining its role in post-stroke recovery.

ADDITIONAL INFORMATION

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