Endur-Hypox

Short version

NCT06714435

N° 2023-A01443-42

Version n° 2 du 11/06/2025

Title	**ENDUR-HYPOX** The Effect of Intermittent Hypoxia on Ventilatory Endurance in Healthy Volunteers
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Rationale / Background	In our daily lives, each of us engages in physical activity of varying intensity. This ability to sustain prolonged submaximal physical exertion corresponds to the physiological concept of endurance. This endurance is a very important yet underestimated determinant of patient morbidity. Patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) are mostly intolerant to exercise. The frequent nocturnal intermittent hypoxia seen in OSAHS could be a cause of this reduced inspiratory endurance due to impaired cortical motor control. Indeed, in addition to its deleterious effects on muscles, intermittent hypoxia may reduce endurance—particularly inspiratory endurance—by impairing cortical motor control, which could precipitate hospitalization during acute respiratory failure. Hypothesis: Intermittent hypoxia reduces inspiratory endurance in healthy volunteers by impairing the respiratory motor cortex's ability to generate effective ventilation
Main Objective	Compare the inspiratory endurance of healthy volunteers after 6 continuous hours of breathing ambient air and after 6 continuous hours of exposure to intermittent hypoxia in a hypoxic chamber.
Primary Evaluation Criterion	The primary outcome measure of the study is the duration, in minutes, of the inspiratory endurance test performed by healthy volunteers. It is assessed under two conditions: normoxia and intermittent hypoxia. The inspiratory endurance test involves applying a load of 30% of each volunteer's maximum inspiratory pressure using a threshold valve. The test will be terminated for the following reasons: - At the volunteer's request. - A maximum test duration of 120 minutes.
Secondary Objectives	Compare, after 6 continuous hours of breathing ambient air and after 6 continuous hours of exposure to intermittent hypoxia in a hypoxic chamber: 1. Maximum inspiratory pressure (Pimax) before and after the inspiratory endurance test.

	2. Inspiratory cortical control measured over the first 15 minutes of the inspiratory endurance test. 3. Inspiratory cortical control measured over the last 15 minutes of the inspiratory endurance test. 4. EVAir at the start of the test 5. Time to onset of respiratory discomfort during the inspiratory endurance test. 6. Sensory perception of inspiratory effort. Compare under ambient air conditions or intermittent hypoxia: 7. The quantity and phenotype of circulating microvesicles. 8. Systolic pulmonary artery pressure and echocardiographic signs of right ventricular function.
Secondary Evaluation Criteria	1. The maximum PImax value in cmH_2O among 8 measurements taken before the endurance test. The same assessment is performed after the test. The difference between the PImax values (before and after the test) will also be considered. 2. The amplitude in µV of the inspiratory premotor potentials (PPI) during the first 15 minutes of the endurance test. Calculated from the EEG tracings using the consensus method. 3. The amplitude in µV of inspiratory premotor potentials (PPI) during the last 15 minutes of the endurance test. 4. EVAir value (0 = no discomfort and 10 = maximum discomfort) at the start of the endurance test. 5. The duration in minutes until respiratory discomfort, defined as an EVAir ≥ 80% of the maximum EVAir for each volunteer. Measurements are taken every 10 minutes during the endurance test by administering an EVA. 6. Scores for each item of the Multidimensional Dyspnea Profile questionnaire, rated by the volunteers following the endurance test. 7. Concentration and phenotype of circulating microvesicles. Assessed based on blood samples collected. 8. The transthoracic echocardiograms performed during the visits will allow measurement of each of the following parameters: maximum tricuspid regurgitation velocity in m/s, systolic blood pressure in mmHg, cardiac chamber surface area in cm^2, ventricular diameter in cm, right ventricular function estimated by the peak S-wave velocity (in cm/sec), systolic excursion of the tricuspid annular plane (TAPSE) in mm, subaortic time-velocity integral in cm, maximum and minimum diameters of the inferior vena cava in mm, left ventricular ejection fraction in %, and pulmonary acceleration time in ms.
Ancillary objective	Compare the sleepiness of healthy volunteers after 6 continuous hours of breathing ambient air and after 6 continuous hours of exposure to intermittent hypoxia in a hypoxic chamber.
Ancillary Judgment Criteria	Number of micro-sleep episodes lasting at least 3 seconds (stages N1, N2, N3, REM) identified in the EEG tracings recorded under both conditions.
Clinical trial design	This is a prospective, interventional, comparative, crossover, single-blind, randomized, single-center study in healthy volunteers.

Inclusion Criteria	- Healthy adults aged 25 to 40 - Not heavy coffee drinkers (< 3 espressos per day) - Non-smokers or those who have quit for at least 3 months and have a total annual consumption of < 10 packs - With a BMI between 18 and 25 kg/m² - Enrolled in Social Security or covered through a third party - Providing free, informed, and signed consent after receiving clear and honest information about the study.
Exclusion Criteria	- History of respiratory or ENT conditions (asthma, chronic bronchitis, COPD, respiratory allergies, swallowing disorders, oropharyngeal malformations, obstructive or central sleep apnea-hypopnea syndrome, alveolar hypoventilation syndrome) - Respiratory, cardiovascular, muscular, or neurological conditions or disorders, or diabetes - Raynaud's disease/syndrome - History of epilepsy or episodes of dizziness suggestive of epilepsy - Psychiatric history requiring hospitalization - Liver failure - Kidney failure - History of acute mountain sickness (presence during or following a stay at high altitude of symptoms such as dizziness, headache, nausea/vomiting, and debilitating fatigue: Lake Louise score > 0) - History of migraines - Taking medications that interfere with respiratory or cardiovascular function, or taking psychotropic medications (anxiolytics, sedatives, antidepressants, neuroleptics, muscle relaxants, etc.) - Alcohol dependence or substance abuse - Anemia, sickle cell disease - SpO2 < 97% at rest in room air - Currently participating in another clinical trial - A protected person as defined in Articles L1121-5 to 8 (persons entitled to enhanced protection, namely minors, persons deprived of liberty by a judicial or administrative decision, pregnant or breastfeeding women, persons residing in a health or social care facility, adults under legal guardianship, and finally patients in emergency situations). - Women of childbearing age who are not using effective contraception (hormonal/mechanical: oral, injectable, transdermal, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy).
Exclusion Criteria	- Incidental finding of acute mountain sickness (Lake Louise score >0) - Pregnant woman (incidental finding) - Persistent average sleep duration < 6 hours - Irreversible deterioration in the volunteer's health within the study period - Unusable electroencephalogram signal

Procedures	Neurophysiological, ventilatory, and cardiovascular functional tests will be conducted under normal conditions (control condition) and under intermittent hypoxia conditions (test condition). Control condition: 6 hours in ambient air with a simulated reoxygenation cycle to maintain the volunteer's blinded status. Test condition, intermittent hypoxia: for 1/3 of the cycle, the SpO2 target is between 85% and 90%, and for 2/3 of the cycle, oxygenation at 1 L/min (with possible subject-dependent adjustments) for a SpO2 target > 95%. One cycle lasts 6 minutes. Randomization assigned groups as follows: Group 1 => Control visit under normoxic conditions at V1, followed by a test visit under intermittent hypoxia at V2 Group 2 => Test visit under intermittent hypoxia at V1, followed by a control visit under normoxic conditions at V2 In both the control and test conditions, there will be a clinical examination to rule out contraindications to hypoxia, a hemoglobin test, 2 transthoracic echocardiograms, 3 blood draws of 30 mL each, completion of the EVAir and Multidimensional Dyspnea Profile questionnaires, as well as a ventilatory endurance test with a valve set at 30% of PImax under EEG recording (applied only for the duration of the test) The volunteer will be monitored throughout the procedure (for the purpose of early detection of any risk of harm and to ensure the volunteer remains alert) via ECG, ActiWave, pulse oximetry, and blood pressure monitoring.
Study size	23 evaluable volunteers (out of a total of 32 recruited volunteers)
Duration of the clinical trial	Duration of the enrollment period: 20 months Duration of participation for each participant: 4 months Total duration of the study: 24 months
Statistical analysis of data	The primary outcome measure (duration of the endurance test) will be presented as a median [Q1, Q3] and will be compared between the two test conditions using a Student's t-test for paired data.
Expected benefits	A better understanding of the effect of intermittent hypoxia on inspiratory endurance and motor control in the brain.