HI-LOOP Study

Protocol summary

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French Research Ethics Committee Number	ID-RCB 2025-A02282-47 (initial approval: 5 February 2026)
Clinical Trials Number	NCT07409649
Title	Influence of intermittent hypoxemia on Loop Gain in healthy subjects (HI-LOOP)
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Coordinating investigator	Vanessa BIRONNEAU Pulmonology Department Poitiers University Hospital
Rationale	Sleep apnoea hypopnoea syndrome (SAHOS) is responsible for a number of co-morbidities, notably cardiovascular, and is currently widespread throughout the world, with significant healthcare costs. Current research in this field focuses on exploring different phenotypes in patients with the disease, in order to be able to offer increasingly personalised care. Several mechanisms can contribute to the development of obstructive sleep apnoea hypopnoea syndrome (OSAH), including ventilatory control, which can be assessed using Loop Gain. In addition, the various mechanisms contributing to the occurrence of different phenotypes in the context of OSAH depends on an endothelial response mediated by extracellular vesicles, which play a role in intercellular communication and which, in the context of OSAH, are responsible for vascular hyperreactivity in response to intermittent hypoxia. As part of our protocol, we would like to study ventilatory control via Loop Gain in intermittent hypoxia with study of the phenotype of microvesicles in healthy subjects in order to better elucidate the mechanisms contributing to the onset of sleep apnoea in the absence of confounding factors (obesity, cardiovascular pathologies, etc.).
Objectives	Primary objective To evaluate the effect of hypoxemia conditions during 6 hours on the Loop Gain in healthy volunteers. Secondary objectives

	1) To compare the evolutions of the controller gain and plant gain between hypoxia condition and ambient air condition. 2) To compare the change in the quantity of extracellular vesicles between hypoxia condition and ambient air condition. 3) To evaluate the correlation between the change in quantity of extracellular vesicles and the evolution of the loop gain, by distinguishing between subjects exposed to intermittent hypoxia and ambient air. 4) To compare the evolution of the loop gain between hypoxia condition and ambient air condition, by distinguishing subjects with or without hyperventilation syndrome.
Endpoints	Primary endpoint The difference between the average values (over 5 minutes) of the loop gain before and after 6 hours of experimental condition. The loop gain is defined as the product of the plant gain and controller gain. Secondary endpoints 1) The evolution of the controller gain (respectively plant gain) is defined as the difference between the average values (over 5 minutes) of the controller gain (respectively plant gain) before and after 6 hours of experimental condition. 2) The change in the quantity of extracellular vesicles is defined as the difference between before and after experimentation for each of the following extracellular vesicles: CD41, CD235a, CD45, CD146, CD66b, CD11b, CD62L CD62E, CD62P, CD62P/platelets ratio, CD162, annexin V. 3) Change in quantity of extracellular vesicles is defined in the secondary endpoint #2. Evolution of the loop gain is defined in the primary endpoint. 4) Definition of the evolution of the loop gain is given in the primary endpoint. The hyperventilation syndrome will be determined by a Nijmegen score upper or equal to 23 calculated at the inclusion visit.
Study design	Single-centre, randomized, crossover, single-blind trial conducted in healthy volunteers. • Test experimental condition: intermittent hypoxia application via hypoxia chamber for 6 hours. • Control experimental condition: ambient air for 6 hours.

	Randomization will be used to determine the order in which each subject will participate over the two visits (after eligibility confirmation): - Arm A: control experimental condition, then test experimental condition after a wash-out period of 7 to 28 days. - Arm B: test experimental condition, then control experimental condition after a wash-out period of 7 to 28 days.
Inclusion criteria	- Healthy volunteer aged [18 – 45] years. - IMC between [18 – 25] kg/m². - No known sleep disorders. - Free subject, without guardianship or curatorship or subordination. - Patient benefiting from a Social Security system. - Having given their informed consent.
Non-inclusion criteria	- Active smoker or quit smoking less than 3 months ago and total consumption of more than 10 packs-years. - Alcohol or drug addiction. - Heavy coffee drinker (>3 espressos per day). - History of acute mountain sickness (presence of symptoms such as vertigo, headache, nausea/vomiting, and incapacitating fatigue during or after a stay at high altitude). - High-altitude living (above 3,000 meters, continuously for more than 6 months during the last 10 years). - History of respiratory disease and/or cardiovascular and/or renal and/or neurological disease (migraines, epilepsy). - Diabetes. - Anemia, sickle cell disease. - Any medication associated with oxygen metabolism and any psychotropic medication (anxiolytics, sedatives, antidepressants, neuroleptics, muscle relaxants, etc.) that may interfere with motor and respiratory control, muscle strength or sleep quality. - Women of childbearing age without effective contraception. - Concurrent participation in another clinical research study affecting respiratory control or respiratory muscles. - Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision, persons staying in a health or social car institution, adults under legal protection and patients in emergency situations.
Post-inclusion exclusion criteria	- SpO2 < 97% in ambient air at rest. - Detection of pregnancy in women of childbearing age.

	- Detection of acute mountain sickness (Lake Louise score > 0). - Abnormalities in spirometry, ventilatory polygraphy, electrocardiogram, and/or hemoglobinometry prior to randomization. - Ventilation minute signal, PETCO2 or PETO2 unusable. - Irreversible deterioration in the volunteer's health during the study period, likely to affect the experimental conditions.
Interventions/Procedures	Inclusion visit - selection • Inclusion and non-inclusion verification. • Informed consent signature. • Clinical examination, including Lake Louise score and Nijmegen score. • Paraclinical tests, including ECG, hemoglobin measurement, urinalysis, and spirometry. A ventilatory polygraphy will be scheduled and performed at the patient's home. Visit T1 • Randomization. • Clinical examination: measurement of vital signs. • Paraclinical tests, including urinalysis and blood sample #1. • Loop gain measurement #1. • Experimentation in the hypoxia chamber: ambient air or intermittent hypoxia according to the randomized arm. The patient is monitored throughout the experimentation. Loop gain measurement #2. • Blood sample #2. • Lake Louise score. Visit T2 (at least 7 days after visit T1) • Clinical examination: measurement of vital signs. • Paraclinical tests, including urinalysis and blood sample #1. • Loop gain measurement #1. • Experimentation in the hypoxia chamber: ambient air or intermittent hypoxia according to the randomized arm. The patient is monitored throughout the experimentation. Loop gain measurement #2. • Blood sample #2. • Lake Louise score.
Study duration	Inclusion period: 12 months Patient participation: 2 months maximum Total study duration: 14 months
Sample size	40 patients.

Statistical analyses	Baseline characteristics and outcomes will be described in each arm. Continuous variables will be summarized using mean and standard deviation. Categorical variables will be reported as frequencies and percentages in each category. Missing data will be reported. No imputation will be performed. The standardized difference will be used to assess the baseline comparability of the two arms. The interaction between the experimental condition and the period will be tested using a mixed model for each outcome to verify that there is no effect related to the order of experimental conditions. A linear mixed model approach will be used to estimate the difference between the primary outcome measured in the two compared groups (test and control experimental conditions). The experimental condition and the period will be included as fixed effects and the subject will be included as random effect to account for within-subject correlations arising from the cross-over design. Statistical significance will be achieved for p-values < 5% by using two-sided alternative hypotheses.