Effects of oxygen status on Hypoxia Inducible Factor 1-α. A pilot proof of principle study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38504

Source
ToetsingOnline

Brief title
Oxygen status and Hypoxia Inducible Factor 1-α

Condition

- Other condition
- Immune disorders NEC
- Ancillary infectious topics

Synonym
infection in the blood, sepsis

Health condition

sepsis

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Hypoxia Inducible Factor 1-&alfa, Inflammation, Innate immunity, Oxygen

Outcome measures

Primary outcome

The main study endpoint is the difference in HIF1α mRNA in circulating

leukocytes between hypoxia and hyperoxia.

Secondary outcome

Secondary objectives are HIF1α protein and aHIF mRNA expression in circulating

leukocytes, measures of ROS, and plasma levels of inflammatory cytokines.

Study description

Background summary

Oxygen is a widely used therapeutically agent for maintaining adequate tissue oxygen levels in modern medicine. Low oxygen levels (hypoxia) can result in inadequate tissue oxygenation, which can, when all compensation mechanisms fail or are exhausted, result in organ failure. On the other hand, prolonged hyperoxia can be toxic as well; probably due to formation of reactive oxygen species (ROS). Recent in vitro and animal studies have established that oxygen status and the innate immune system are intimately linked.
Hypoxia can exert pro-inflammatory effects, mainly through hypoxia-inducible factor (HIF) of which HIF1α is the most studied, and conversely, inflammation can induce an intracellular hypoxic state due to increased oxygen demand.
On the other hand, hyperoxia is related to immune suppression, as in animal studies, hyperoxia has been shown to attenuate systemic inflammation and improve survival in inflammatory conditions. However, hyperoxia-induced immunosuppression renders animals increased vulnerable to pathogens. In clinical studies, there is conflicting evidence on the effect of hyperoxia on

prevention of surgical site infections, with some reporting a 50% reduction in the incidence of surgical site infections using 80% oxygen, while others report a 100% increased incidence of surgical site infections when using an FiO2 of 80%.
Taken together, permissive hypoxia or hyperoxia may be a cheap, non-pharmacological, non-invasive treatment modality to modulate the innate immune response in a wide variety of inflammatory conditions, such as sepsis. For instance, dampening innate immunity could be beneficial in the early hyperinflammatory phase of sepsis, while stimulation of the innate immune response could represent a novel treatment option to reverse sepsis-induced immunoparalysis, a hyporesponsive state of the immune system frequently encountered in patients after hyperinflammation has waned. However, up till now, most of this evidence has been obtained in in vitro and animal studies, and precise effects of hypoxia and hyperoxia on kinetics of HIF1α, ROS, and innate immunity have only been sparsely studied. Therefore, in the present study we wish to investigate the effect of hypoxia and hyperoxia on the kinetics of HIF1α and ROS as well as measures of innate immunity in healthy volunteers.

Study objective

The primary objective of the study is to determine the effects of hyperoxia and hypoxia in healthy volunteers on kinetics of HIF1α mRNA in circulating leukocytes. Secondary objectives are to determine the effects of hyperoxia and hypoxia on HIF1α protein and aHIF mRNA expression in circulating leukocytes, the induction of ROS, phagocytic function of circulating leukocytes, ex vivo stimulation of leukocyten with diverse inflammator stimuli, the release of inflammatory cytokines, basic hemodynamic and ventilatory parameters, and to evaluate their effects on tissue oxygenation, measured by near infrared spectrometry.

Study design

A parallel, randomized study in healthy male volunteers. The subjects will be randomized to hypoxia or hyperoxia.

Intervention

In the hypoxia group: the subjects will breathe an individualized mix of nitrogen and room air for three-and-a-half hours using an air-tight respiratory helmet. The gas mixture will be adjusted to achieve a saturation of 80-85%. In the hyperoxia group, subjects will breathe 100% oxygen for three-and-a-half hours using the same respiratory helmet used in the hypoxia group.

Study burden and risks

All subjects will visit the hospital for a screening visit in which a medical interview and physical examination will be carried out (30 minutes). At the screening visit and the day after the experiment blood will be obtained by venapuncture. During the experimental day, subjects will receive an arterial line, placed under local anaesthesia. Furthermore, a venous cannula will be placed for the administration of fluids. The subjects will be exposed to hypoxia or hyperoxia for 3 hours, and will be monitored for 5.5 hour after cessation of hypoxia or hyperoxia. There is a large body of scientific work with induction of hypoxia in healthy human subjects; minor side effects as nausea, headache and light-headedness have been reported after six hours of hypoxia, making the chance of these side effects occurring in the present study (3 hours of hypoxia) very low. There are no reports of damage or discomfort of exposure to hyperoxia. The subjects will wear a respiratory helmet that is approved for regular patient care. A physician or nurse will be present in the experiment room at all times, and subjects will be continuously monitored. In total, approximately 350 ml blood will be drawn during the study, which is comparable to previous experiments, and has never resulted in adverse events. Subjects will not benefit directly from participation to the study. A subject fee is provided.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Age >=18 and <=35
-Male
-Healthy

Exclusion criteria

-Use of any medication, smoking
-History, signs or symptoms of cardiovascular disease, history of atrial or ventricular arrhythmia, (Family) history of myocardial infarction or stroke under the age of 65 years, cardiac conduction abnormalities on the ECG consisting of a 2nd degree atrioventricular block or a complex bundle branch block, hypertension (defined as RR systolic > 160 or RR diastolic > 90), hypotension (defined as RR systolic < 100 or RR diastolic < 50)
-Renal impairment (defined as plasma creatinine >120 µmol/l), Liver enzyme abnormalities alkaline phosphatase>230 U/L and/or ALT>90 U/L
-Medical history of any obvious disease associated with immune deficiency, pre-existent lung disease or asthma
-CRP > 20 mg/L, WBC > 12x109/L, or clinically significant acute illness, including infections, within 4 weeks before endotoxemia day
-Participation in a drug trial or donation of blood 3 months prior to the experiment, use of recreational drugs within 21 days prior to experiment day, visit to altitude >1500m within 4 weeks prior to the experiment, air travel with flight time over 3 hours within 4 weeks prior to the experiment, history of acute mountain sickness, recent hospital admission or surgery with general anaesthesia (<3 months)
-Claustrophobia
-Feelings of discomfort during a 10 minute test wearing the transparent respiratory helmet at the screening visit

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-05-2013
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	25-04-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL43770.091.13
Other	volgt