Effects of moderate intermittent hypoxia exposure on peripheral insulin sensitivity and substrate metabolism in humans

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON42717

Source
ToetsingOnline

Brief title
Moderate intermittent hypoxia exposure

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
adult-onset diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: European Foundation for the Study of Diabetes

Intervention

Keyword: Adipose tissue, Moderate intermittent hypoxia, Obesity, Skeletal muscle

Outcome measures

Primary outcome

- peripheral insulin sensitivity

Secondary outcome

- adipose tissue and skeletal muscle oxygen tension

- hepatic insulin sensitivity

- body weight

- Body Mass Index (BMI)

- body composition (DEXA)

- adipose tissue blood flow

- plasma glucose, insulin, free fatty acids, triacylglycerol, glycerol

concentrations

- blood pressure

- blood oxygen saturation

- hunger and satiety

- energy expenditure and substrate oxidation

- systemic inflammation (e.g. IL-6, leptin, adiponectin, TNFα)

- gene expression in adipose tissue and skeletal muscle

- fat cell size

- adipose tissue and skeletal muscle oxidative capacity

- Glucose uptake by adipocytes and myotubes

Study description

Background summary

The obesity epidemic calls for novel strategies to prevent and treat obesity and its comorbidities. Several studies have indicated that the amount of oxygen to which tissues are exposed may substantially impact cardiometabolic health. Interestingly, living at high altitude (hypobaric hypoxia) seems to be associated with improved glucose homeostasis and a decreased prevalence of type 2 diabetes. Furthermore, normobaric hypoxia exposure has been shown to exert beneficial effects on glucose homeostasis and insulin sensitivity in rodents and humans. This may, at least in part, be explained by the effects of altered adipose tissue and skeletal muscle oxygen tension. The present study aims to investigate the effects of moderate intermittent hypoxia exposure on whole-body and tissue-specific insulin sensitivity and substrate metabolism in humans, and potential underlying mechanisms (adipose tissue and skeletal muscle oxygen tension, oxidative capacity and inflammation) will be examined. This study may open up a novel therapeutic avenue with direct clinical relevance for obese insulin resistant subjects.

Study objective

The current research proposal intends to study the therapeutic potential of moderate intermittent hypoxia (IH) exposure in subjects at high risk of developing type 2 diabetes, and aims to address the following key objectives:
1) To investigate the effects of moderate IH exposure for 7 consecutive days on whole-body and tissue-specific insulin sensitivity, substrate metabolism, adipose tissue and skeletal muscle mitochondrial capacity and PO2 in obese insulin resistant men.
2) To unravel the mechanisms underlying the effects of moderate IH exposure on insulin sensitivity, mitochondrial function, and glucose uptake using differentiated human adipose tissue-derived mesenchymal stem cells (hMSC) and skeletal muscle satellite cells.
3) To elucidate the effects of moderate IH exposure on adipose tissue and systemic inflammation.

Study design

We will perform a randomized, placebo-controlled, cross-over study to investigate the effects of moderate intermittent hypoxia exposure on whole-body and tissue-specific insulin sensitivity and substrate metabolism in humans, and examine potential underlying mechanisms (adipose tissue and skeletal muscle oxygen tension, oxidative capacity and inflammation). Therefore, subjects will be exposed to 1) moderate intermittent hypoxia (15% O2; equivalent to ~2400m above sea level) and 2) normoxia (21% O2) for 7 consecutive days (3 cycles of

2h exposure/d in a normobaric room, with 1h of normoxia exposure between hypoxic cycles) in a randomized fashion (computer-generated randomization plan; block size, n=4), separated by a 4 week wash-out period.
After initial screening, subjects are asked to visit the university for two periods of 7 consecutive days with a wash-out period of 4 weeks (Table 1, for details please see *Methods* * *Study procedures*):
- During the 7 days (time investment: 8 hours/day), subjects will be exposed to 1) moderate intermittent hypoxia (15% O2; equivalent to ~2400m above sea level) and 2) normoxia (21% O2) for 7 consecutive days (3 cycles of 2h exposure/d in a normobaric room, with 1h of normoxia exposure between hypoxic cycles) in a randomized fashion (computer-generated randomization plan; block size, n=4), separated by a 4 week wash-out period. On days 1, 3, 6 and 7 of treatment, blood samples will be collected to determine circulating metabolite concentrations and systemic inflammatory markers, and a questionnaire to assess hunger and satiety (VAS-scores) has to be completed at days 1, 3 and 7.
- At day 6 (time investment: 8 hours), we will adipose tissue and skeletal muscle PO2 (two-channel optochemical measurement system), adipose tissue blood flow (133Xe wash-out technique).
- At day 7 (time investment: 5 hours), a high-fat mixed-meal test will be performed to determine fasting and postprandial metabolite concentrations, substrate metabolism (indirect calorimetry) and systemic inflammatory markers
- At day 8 (time investment: 8 hours), peripheral and hepatic insulin sensitivity will be determined (2-step hyperinsulinemic-euglycemic clamp) and skeletal muscle (m. vastus lateralis) and adipose tissue biopsies will be collected at baseline and during insulin-stimulated conditions (steady-state of the clamp).
Thus, after initial screening and BMR measurement and DEXA scan, subjects will have to invest approximately 106 hours for the total study.

Intervention

Exposure to 15% O2 is comparable to an altitude of ~2800 m. Adverse Events (e.g. Acute mountain sickness symptoms) may occur above ~2500 m, although most people do not experience symptoms at this altitude. Importantly, the exposure to normobaric moderate hypoxia (15% O2) will be under strict control, as described in detail in section 12.1.
Each subject will undergo two exposure regimens, in a randomized fashion, with a 4-week wash-out period in between:
- 7 consecutive days of intermittent exposure to 15% O2 (intervention condition)
- 7 consecutive days of 21% O2 exposure (control condition)

Study burden and risks

- During several visits blood samples will be collected via a catheter. Occasionally, a local hematoma or bruise may occur. Some participants report

pain during insertion of a catheter.
- During the visits at day 5 (twice because of the cross-over design), a microdialysis probe will be placed in the abdominal subcutaneous adipose tissue under sterile conditions 6-8 cm lateral from the umbilicus. One hour before insertion of the probe, the skin will be anaesthetised by means of a cream containing lidocaine (25 mg/g) and prolocaine (25 mg/g) (EMLA, Astra Pharmaceutica, Zoetermeer, The Netherlands). The microdialysis catheter will be inserted in skeletal muscle (gastrocnemius muscle) under local anesthesia. Insertion of the microdialysis probes is as good as painless.
- Due to local anesthesia, the adipose tissue and skeletal muscle biopsies are as good as painless. Subjects may experience some discomfort (pressure during the introduction of the needle) during the muscle biopsy procedure. Occasionally, desensitization or increased sensitivity of the skin at the site of the muscle biopsy may occur, which may last for several weeks/months. Furthermore, the biopsy procedures may cause a local hematoma or bruise. To minimize the risk of hemotoma, the muscle biopsy place will be taped with an elastic adhesive compression bandage, and the adipose tissue biopsy place will be compressed for at least 5min after the biopsy has been taken. The place of incision will leave a small scar, which will be minimized by sealing the incision with sterile steristrips and a waterproof bandaid.
- The total radiation exposure (effective dose) during this research (including 133Xe and DEXA scan) is 0.09 mSv (4% of total background radiation in the Netherlands per year).
- Exposure to 15% O2 (~2800 m) rather than lower PO2 will be applied to prevent or at least minimize Adverse Events. Acute mountain sickness symptoms (e.g. headache, nausea) may occur above ~2500 m, although most people do not experience symptoms at this altitude. This will be monitored using the Lake Louise Acute Mountain Sickness (AMS) score questionnaire. To ensure that moderate intermittent hypoxia exposure will not cause adverse effects, oxygen saturation (Sp,o2, %) will be monitored continuously throughout the exposure regimen by means of finger pulse oximetry, and blood pressure will be monitored each day (automatic inflatable cuff; Omron Healthcare, Hamburg, Germany).

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

Males with overweight/obesity (body mass index >= 28 kg/m2) - insulin resistant (HOMA>=2.2) - Age: 30-65 - Non smoking - A stable bodyweight for at least 3 months (no change in bodyweight: <3kg)

Exclusion criteria

cardiovascular disease (determined by questionnaire, electrocardiogram (ECG), blood pressure (subjects with moderate to severe hypertension (grade 2 or 3 based on WHO criteria) will be excluded from participation in this study (SBP >160 mmHg, DBP > 100 mmHg)), type 2 diabetes mellitus, cancer, asthma or bronchitis, obstructive sleep apnea (OSAS), liver or kidney malfunction (determined based on ALAT and creatinine levels, respectively), disease with a life expectancy shorter then 5 years (subjects will be asked if they have a disease, which could lead to death within 5yr) diagnosis, abuse of products (alcohol consumption > 15 units/week), smoking, plans to lose weight (subjects will be asked if they have weight loss plans (e.g. to increase their physical activity level or change diet): a positive answer will lead to exclusion) or follow a hypocaloric diet, participation in organized sports activities more than three hours a week, use of high doses of anti-oxidant vitamins (A, C, E, β-carotene; a standard multi-vitamin capsule is permitted if less than 800µg/day Vit A, 60mg/day Vit C, 10mg/day Vit E and 400µg/day β-carotene) or use of any medication that influences glucose metabolism and inflammation

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-04-2016
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 29164
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL54685.068.15
OMON	NL-OMON29164