The influence of breathing techniques and exposure to cold on inflammation during human endotoxemia, an explorative study

Published: 11-04-2016
Last updated: 14-12-2024

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Ethical review	Approved WMO
Status	Completed
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON43078

Source
ToetsingOnline

Brief title
EXPOCOL

Condition

- Autoimmune disorders
- Ancillary infectious topics

Synonym
RA, reumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Intensive Care
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cold exposure, endotoxin, hyperventilation, inflammation

Outcome measures

Primary outcome

The main study endpoint is the difference in circulating TNF-α over time

following LPS administration between groups

Secondary outcome

Differences between groups in:

- Levels of other circulating cytokines (including, but not limited to IL-6,

IL-10 and IL-1RA)

- Plasma adrenaline levels

- Plasma cortisol levels

- Blood gas parameters

- Mitochondrial oxygen tension

- Metabolome

- Body temperature

- Illness score

- Hemodynamic parameters (heart rate, blood pressure)

- Leukocyte counts and differentiation

- Pain thresholds

- Presence of TLR ligands in plasma

- HSP70 levels in plasma.

- Production of inflammatory mediators by ex vivo-stimulated leukocytes

- Inflammatory transcriptional pathways (by use of qPCR/microarrays/RNA

sequencing

- Heart rate variability

Study description

Background summary

Inflammatory cytokines play a pivotal role in rheumatoid arthritis (RA) and innovative non-pharmacological therapies aimed at limiting cytokine production are highly warranted. Recently, our group showed that healthy volunteers trained in an intervention developed by *Iceman* Wim Hof were able to voluntarily attenuate the pro-inflammatory response during experimental human endotoxemia (a model of systemic inflammation elicited by administration of lipopolysaccharide [LPS] in healthy volunteers). Subjects trained in the intervention exhibited profound increases in plasma adrenaline levels, a rapid increase of an anti-inflammatory cytokine and subsequent attenuation of the pro-inflammatory response. This intervention could therefore represent a treatment modality that would empower RA patients to exert self-control over their disease.
The intervention consists of three elements, namely meditation, exposure to cold and breathing techniques. The meditation element is not likely to be involved. It was a very minor part of the training program and was not practiced during the endotoxemia experiments. Exposure to cold and the subsequent rewarming to normal body temperature may influence the inflammatory response through the release of immunomodulatory molecules like HSP-70. Also, exposure to cold can induce an ischemia-reperfusion-like state in the skin and peripheral tissue that is known to be involved in the downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines. We anticipate that the third element, breathing techniques, is the major contributor to the anti-inflammatory effects of the intervention previously observed. Subjects and Hof practiced two types of breathing techniques. In our latest study (yet unpublished data, CMO 2014-1374), we investigated the effects of these two breathing techniques in the absence of cold exposure (or meditation) on plasma adrenaline levels, which we found to be strongly correlated with the anti-inflammatory effects previously found. The present study aims to explore the effects of two of those elements of the intervention developed by Hof, namely the breathing technique (*strength ventilation*) and

the exposure to cold, on the immune response during human endotoxemia.

Study objective

The primary objective of the present study is to determine the effects of the `strength ventilation` breathing technique and exposure to cold, both separately and in combination, on the inflammatory response during human endotoxemia. To this end, we will employ a 2 by 2 design. Additionally, we want to evaluate the influence of the cold exposure and breathing technique on pain thresholds and oxygen tension in the mitochondria.

Study design

A parallel randomized controlled explorative study in healthy male volunteers during experimental endotoxemia.

Intervention

a cold exposure course and training in *Strength Ventilation* breathing technique in various modalities:
1. `Cold Exposure` group. A group of subjects (n=12) that will receive an extensive cold exposure course.
2. ` Strength Ventilation` group. A group of subjects (n=12) that will be trained in the Strength Ventilation breathing technique.
3. `Cold Exposure and Strength Ventilation` group. A group of subjects (n=12) that will receive both the cold exposure and the training in the *Strength Ventilation* breathing technique .
4. `Control` group. A group of subjects (n=12) that will only participate in the endotoxemia experiment.

Study burden and risks

The burden of the study procedures consist of the time investment related to the training procedures and a maximum of three visits to the hospital. All subjects will visit the hospital for a 60-minute screening visit (medical interview, physical examination, venapuncture, pain threshold measurement) and a 45 minute baseline visit. Subjects participating in the cold exposure course will visit the training facility four days in a row and subsequently expose themselves to daily cold showers. Subjects participating in the *Strength Ventilation* breathing training visit the training facility once for 2 hours. For the endotoxemia experiment day, all subjects will be admitted to the research intensive care unit for 10 hours.

The training methods developed by Hof have been applied to hundreds of volunteers in the past. These include not only healthy persons, but also more than 100 patients with varying illnesses. No problems or emergencies have ever

arisen in healthy persons or patients. The training will be given by the study team by an MD from the Radboudumc department of Intensive Care Medicine. The study team is medically responsible for the subjects during the training and will supervise every part of the training. Importantly, during the training, subjects will not be forced in any way to expose themselves to cold any longer than they wish to. The training is specifically targeted at moving a person`s boundaries within his own capabilities.

On the endotoxemia experiment day, subjects will be admitted to the research intensive care unit for 10 hours. An arterial catheter (under local anesthesia), and a intravenous catheter will be placed. The administration of LPS induces flu-like symptoms for approximately 4-6 hrs. This model of systemic inflammation has been applied for more than 10 years in our department and thousands of subjects worldwide have participated in endotoxemia trials. During the endotoxemia experiment day, subjects will be under constant supervision of an experienced intensivist with continuous monitoring of blood pressure and heart rate. The endotoxemia protocol and associated risks are identical to earlier endotoxemia studies performed in our institute. In total, a maximum of 400 ml blood will be drawn during the study, which is comparable to previous studies and never resulted in adverse events. Subjects will not benefit directly from participation to the study. A subject fee is provided.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Written informed consent
Age >=18 and <=35 yrs
Male
Healthy

Exclusion criteria

Prior experience with any of the elements of the intervention developed by Hof;Prior experience with other breathing, meditation, or cold exposure techniques;Use of any medication;Smoking;History of asthma;Previous spontaneous vagal collapse;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 creatinin >120 µmol/l);Liver enzyme abnormalities;Medical history of any disease associated with immune deficiency;CRP > 20 mg/L, WBC > 12x109/L, or clinically significant acute illness, including infections, within;4 weeks before endotoxin administration;Participation in a drug trial or donation of blood 3 months prior to the LPS challenge;Use of recreational drugs within 7 days prior to endotoxemia experiment day;Recent hospital admission or surgery with general anaesthesia (<3 months)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-04-2016
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO

Date:	11-04-2016
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
Other	Clincial Trials.gov - nummer nog niet bekend
EudraCT	EUCTR2016-000513-75-NL
CCMO	NL56686.091.16