Increasing plasma adrenaline levels through breathing techniques - an explorative study

Published: 27-11-2014
Last updated: 21-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON41858

Source
ToetsingOnline

Brief title
INADRI

Condition

- Autoimmune disorders

Synonym
RA, reumatoid arthritis

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: Acid/base balance, Adrenaline, Hyperventilation, Hypoventilation

Outcome measures

Primary outcome

The main study parameter is plasma adrenaline concentration. Our primary endpoint is the difference between plasma adrenaline levels during the hyper/hypoventilation technique and the strength ventilation technique within the HTR group.

Secondary outcome

- Difference between plasma adrenaline levels during the hyper/hypoventilation technique and plasma adrenaline levels during the strength ventilation technique within the EIN and SIN groups.
- Differences in plasma adrenaline levels during hyper/hypoventilation or strength ventilation between HTR, EIN, and SIN groups.
- Differences in the following parameters between hyper/hypoventilation and strength ventilation within HTR, EIN, and SIN groups as well as differences during hyper/hypoventilation or strength ventilation between HTR, EIN, and SIN groups.

o Plasma IL-10 concentration

o Body temperature

o Hemodynamic parameters (heart rate, blood pressure)

o Leukocyte counts and differentiation

o Cortisol (hair and plasma)

o Other catecholamine*s (including noradrenaline)

o Heart rate variability

o Blood gas parameters

Pain thresholds before start training/instruction and at the end of the

experimental day, objectified with Quantative Sensory Testing

Study description

Background summary

Auto-immune diseases are characterized by an inappropriate inflammatory response against tissues in the body. These diseases, of which rheumatoid arthritis (RA) is the most well-known, represent a major health care burden. Pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β are central in the pathophysiology of many auto-immune diseases [1, 2], and biologics that antagonize inflammatory cytokines or their receptors, e.g. anti-TNF-α, soluble TNF-α-receptor, anti-IL-6 receptor, and IL-1 receptor antagonist, are very effective treatments [3, 4]. However, they are very expensive and can have serious side effects [5, 6]. Therefore, innovative therapies aimed at limiting inflammatory cytokine production in a more physiological manner are warranted.

The sympathetic nervous system, a part of the autonomic nervous system (ANS), can limit the inflammatory response via activation of β2-adrenoceptors by catecholamines such as (nor)epinephrine [7, 8]. In addition, as part of a stress response increased levels of catecholamines are often accompanied by elevations of the well-known immunodepressant cortisol (via activation of the hypothalamic-pituitary-adrenal [HPA] axis)[9, 10]. Next to pharmacological modulation of the sympathetic nervous system, for instance by administration of catecholamines [7, 8], it can be envisioned that endogenous modulation of sympathetic activity may also result in attenuation of the inflammatory response. Which in turn could represent a treatment modality that would empower RA patients to exert self-control over their disease activity. However, both the ANS and the inflammatory response are generally regarded as systems that cannot be voluntarily influenced. Nevertheless, results from two of our recent endotoxemia studies into the effects of techniques developed by *iceman* Wim Hof (cold exposure, meditation and breathing techniques) demonstrate that through these techniques it is indeed possible to voluntarily activate the sympathetic nervous system [11, 12]. This is reflected by profound increases in

plasma adrenaline levels, a rapid increase of the anti-inflammatory cytokine IL-10, and subsequent attenuation of the pro-inflammatory response [11].

Ultimately, we want to translate these findings into novel treatment options for autoimmune diseases such as RA. However, it would be of major benefit if patients would only have to learn/practice one of the techniques instead of all three. For instance, the cold exposure is very demanding, might exposure patients to unnecessary risk, or may not be suitable for patients at all. Furthermore, it remains to be determined whether the techniques can only be taught by Hof and if an extensive training is necessary at all. Answering these questions is pivotal because identification of the optimal technique(s) as well as objectifying and standardizing Hof*s methods will aid future research in this field and ultimately facilitate development of clinical protocols.

Strikingly, although having been taught all three techniques, in both studies subjects predominantly practiced a hyper/hypoventilation technique during the endotoxemia experiment, characterized by cycles of hyperventilation followed by breath retention [11, 12]. This resulted in intermittent hypoxia and profound shifts in acid/base balance. However, approximately 1 hour after LPS administration the subjects also practiced another breathing technique consisting of deep inhalations and exhalations in which every in- and exhalation was followed by breath holding for 10 seconds during which all muscles were tightened (*strength ventilation*).

Based on these observations, we hypothesize that these breathing techniques are responsible for the increase in plasma adrenaline levels and the subsequent dampened immune response, because during the endotoxemia experiments the subjects solely practiced these techniques, and were not exposed to cold or practiced meditation [11, 12]. More specifically, we suspect that the hyper/hypoventilation technique accounts for the observed effects. This is supported by studies that have shown that both hyperventilation [13, 14] as well as hypoxia [15, 16] (which occurred in our subjects during the hypoventilation phase [11]) result in increased plasma adrenaline levels. However, effects of the strength ventilation on adrenaline induction cannot be ruled out.

Study objective

Therefore, the primary objective of the present study is to investigate whether the hyper/hypoventilation or the strength ventilation technique accounts for the observed increase in plasma adrenaline levels. Furthermore, we want to determine whether it is mandatory that subjects are trained by Hof and whether extensive training is necessary at all.

Study design

A parallel randomized study in 36 healthy male volunteers

Subjects will be randomized to either
1. The `hoftraining` group (HTR): a group of subjects (n=12) that will be trained extensively by Hof and his team in both hyper/hypoventilation and strength ventilation breathing techniques.
2. The `extensive instruction` group (EIN): a group of subjects (n=12) that will receive an extensive instruction course supervised by the research team in both hyper/hypoventilation and strength ventilation breathing techniques.
3. The `short instruction` group (SIN): a group of subjects (n=12) that is trained for 1 hour on the day before the experiment by the research team in both hyper/hypoventilation and strength ventilation breathing techniques.

Study burden and risks

The burden of auto-immune diseases is enormous, both from a clinical and economical perspective. The most well-known auto-immune disease, rheumatoid arthritis, is characterized by pain and swelling, joint damage and progressive disability, which greatly affects quality of life. In the Netherlands in 2007, approximately 165000 patients suffered from rheumatoid arthritis, of which the healthcare costs were more than 200 million Euros (source: Nationaal kompas volksgezondheid). The estimated revenue loss due to working incapactity and sick leave for rheumatoid arthritis are estimated at several billion Euros. Due to population growth and increasing age of the population, the prevalence of rheumatoid arthritis is estimated to increase considerably over the next decades (source: Nationaal kompas volksgezondheid). Novel therapies for autoimmune diseases like rheumatoid arthritis are therefore highly warranted. The therapy investigated in this study could represent a novel, non-invasive, cheap method to reduce disease progression. Furthermore, it is a therapy that, if effective, greatly increases self-management of autoimmune diseases. An increase in patient empowerment is highly warranted, especially in chronic autoimmune diseases.

Results from two of our recent studies demonstrate that this is possible through techniques developed by *iceman* Wim Hof, namely meditation, exposure to cold, and breathing exercises. Hof himself and healthy volunteers trained by him were able to voluntarily activate the sympathetic nervous system, resulting in adrenaline release and subsequent suppression of the inflammatory response during experimental human endotoxemia (a model of systemic inflammation elicited by administration of lipopolysaccharide [LPS] in healthy volunteers). Also, the reported subjective symptom score was lower which further supports the beneficiary effects of the learned techniques.

The burden of the study procedures consists 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 screening visit in which a medical interview, physical examination, and blood withdrawal by vena puncture will be

carried out (30 minutes). For the baseline measurements before start of the training program/instruction (QST, catecholamine*s/cortisol, cytokines, heart rate variability), subjects will visit the hospital for 50 minutes. During the experiment day, subjects will be hospitalized for approximately 7 hours. An arterial line will be placed under local anaesthesia using 2% lidocaine. Furthermore, a venous cannula will be placed.

We feel that the risk to, and burden for the subjects are in proportion to the potential value of the research.

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 yrs

- Male
- Healthy

Exclusion criteria

- Experience with the methods of Wim Hof and his team or other breathing techniques
- Use of any medication
- Smoking
- Use of recreational drugs within 21 days prior to the experiment day
- Use of caffeine or alcohol within 1 day prior to the experimental day.
- Surgery or trauma with significant blood loss or blood donation within 3 months prior to the experimental day.
- Participation in another clinical trial within 3 months prior to the experimental day.
- History, signs, or symptoms of cardiovascular disease
- History of atrial or ventricular arrhythmia
- Hypertension (RR systolic >160 or RR diastolic >90)
- Hypotension (RR systolic <100 or RR diastolic <50)
- Conduction abnormalities on the ECG consisting of a 1st degree atrioventricular block or a complex bundle branch block
- History of asthma
- CRP > 20 mg/L, WBC > 12x109/L, or clinically significant acute illness, including infections, within 4 weeks before the experimental day.

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-12-2014

Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	27-11-2014
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	Clinicaltrials.gov (nr. volgt)
CCMO	NL51237.091.14