Methodological trial to investigate the dose-response relationship, test-retest reliability and tolerance to repeated exposure of the 35% carbon dioxide experimental panic challenge in CO2-sensitive healthy volunteers

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To investigate the dose-response relationship, test-retest reliability and tolerance to repeated exposure of the 35% carbon dioxide experimental panic challenge in CO2-sensitive healthy volunteers as measured with the PSL-IV total Score, VAS Fear,...

Ethical review	Approved WMO
Status	Completed
Health condition type	Anxiety disorders and symptoms
Study type	Observational invasive

Summary

ID

NL-OMON53268

Source
ToetsingOnline

Brief title
Methodological optimization of the CO2 challenge

Condition

- Anxiety disorders and symptoms

Synonym
anxiety disorders, Panic disorders

Research involving

Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Centre for Human Drug Research (CHDR)

Intervention

Keyword: CO2 inhalation, Panic disorder

Outcome measures

Primary outcome

This study aims to illuminate the primary endpoints of the following three objectives as follows:

1. The objective is to discern and contrast the frequency and intensity of panic attacks induced by a single vs. a double vital capacity inhalation of 35% CO2/65% O2. We will accomplish this by quantifying the difference in pre- and post-CO2 challenge metrics - namely PSL-IV, VAS Fear, and VAS Discomfort. The goal is to reveal any statistically significant distinctions in the frequency and intensity of panic reactions between these two inhalation scenarios.

2. The objective is to scrutinize the consistency and reliability of panic reactions induced by the repeated inhalation of double vital capacity 35% CO2/65% O2 in CO2-sensitive, healthy volunteers. We will accomplish this by quantifying the difference in pre- and post-CO2 challenge metrics - specifically PSL-IV, VAS Fear, and VAS Discomfort, between the initial and subsequent inhalation tests. The goal is to determine whether repeated

exposures yield statistically significant consistency in the frequency and intensity of panic responses among the study participants.

3. The objective is to discern and contrast the persistence of sensitivity to the panicogenic effects of CO2 in healthy participants, previously identified as CO2-sensitive, over an extended period. We plan to accomplish this by quantifying the variation in pre- and post-CO2 challenge metrics, specifically PSL-IV, VAS Fear, and VAS Discomfort, between these two timepoints - initial assessment and years later. The ultimate aim is to establish whether there exist statistically significant distinctions in the frequency and intensity of panic reactions over time, indicating a maintained sensitivity or alteration to the CO2 challenge.

Secondary outcome

• Explore the effects of single and (repeated) double breath 35% CO2/65% O2 on heart rate and blood pressure in CO2-sensitive healthy volunteers.

• Explore the effects of single and (repeated) double breath 35% CO2/65% O2 on neuro-endocrine mediated autonomic nervous system activation and orexin/hypocretin release in CO2-sensitive healthy volunteers.

• Explore the relationship between baseline personality and temperament characteristics and individual response to CO2 in CO2-sensitive healthy volunteers.

Study description

Background summary

The CO2 inhalation model for panic has undergone both technical innovation and relatively extensive validation since the 1980*s.

Panic disorder (PD) patients consistently display the highest sensitivity to CO2, followed by first degree relatives of PD patients and healthy volunteers, which show a concentration dependent sensitivity to inhaled CO2. Additionally, registered anxiolytic drugs administered in clinically effective therapeutic doses reduce CO2 sensitivity in healthy volunteers and patients over time.

Various CO2 regimens have been applied to induce panic attacks (PAs) in human populations. Although both single and double vital capacity inhalations of 35% CO2/65% O2 consistently demonstrate panicogenic effects in healthy volunteers and panic disorder (PD) patients or their first-degree relatives, the CO2 sensitivity of both similar patient and healthy groups tend to vary between research groups.
Since varying CO2 administration protocols which include both single and double vital capacity administrations are being applied across research groups, differences in CO2 sensitivity could very well be the result of unintended methodological variability. The lack of a standardized procedure to test sensitivity to CO2 therefore hampers accurate comparisons between tests performed under different protocols. A better understanding of whether a single or double breath 35% CO2/65% O2 is sufficient to induce PAs is expected to contribute to the validity of acute CO2 inhalation as tool in pathophysiological research and in early CNS drug development.

The differential response to single versus double 35% CO2 vital capacity inhalation of CO2 remains to be examined systematically to further validate it as experimental paradigm for future use. To the best of our knowledge no study has been previously published that compares single and double vital capacity 35% CO2 inhalation in a single study. Therefore, we aim to investigate the panicogenic effects of a single vs. a double vital capacity method 35% CO2 in healthy volunteers. We hypothesize that 35% CO2 double vital capacity inhalation is associated with a higher percentage of subjects experiencing a panic attack compared to single vital capacity inhalation.

Additionally, this study also seeks to systematically investigate the test-retest reliability of the CO2 inhalation challenge in healthy volunteers who are sensitive to the anxiogenic effects of CO2 inhalation. Previous research has only examined intervals of up to a few weeks, leaving it unclear whether individuals who are sensitive to the 35% CO2 inhalation challenge remain sensitive for longer periods, possibly years later.

Finally, this study seeks to investigate whether tolerance or desensitization occurs in healthy volunteers who were previously sensitive to the CO2

challenge. While past research has explored this topic in patients with panic disorders, studies in healthy volunteers who were screened for sensitivity to the anxiogenic effects of CO2 challenges are non-existent. Previous tolerance studies have been conducted in healthy volunteers, but these participants were not selected based on their sensitivity to the anxiogenic effects of CO2 inhalation. If tolerance does not occur after four challenges administered one week apart over the course of a month, this would justify conducting future three-way crossover studies.

Study objective

To investigate the dose-response relationship, test-retest reliability and tolerance to repeated exposure of the 35% carbon dioxide experimental panic challenge in CO2-sensitive healthy volunteers as measured with the PSL-IV total Score, VAS Fear, and VAS Discomfort.

Study design

Five visit trial to investigate the dose-response relationship, test-retest reliability and tolerance to repeated exposure of the 35% carbon dioxide experimental panic challenge in 20 CO2-sensitive healthy volunteers.
Out of the five scheduled visits:
• single or a double vital capacity inhalation of 35% CO2/65% O2 will be randomized over a 2-way cross-over part consisting of visit 1 and visit 2. During the first visit, half of the participants (n=10) will be randomized to receive a single vital capacity inhalation of CO2 while the other half (n=10) will be randomized to double vital capacity inhalation of CO2. Approximately a week later, the groups will switch, with the group originally assigned the single vital capacity inhalation now receiving the double vital capacity inhalation, and vice versa.
• visits 3, 4 and 5 will follow a fixed pattern, with all participants receiving only double vital capacity 35% CO2/65% O2 inhalation roughly a week apart.
On the first day, prior to the CO2 challenge, the Spielberger State-Trait Anxiety Inventory (STAI), Dutch Personality Questionnaire (DPQ), and Cloninger Temperament Character Inventory (TCI) will be administered.
To evaluate the severity of panic symptoms, each subject will complete the PSL-IV , VAS Fear and VAS Discomfort within five minutes before and as soon as possible (but no later than 15 minutes) after the CO2 challenge. In addition, the STAI Y1 will be administered within 20 minutes before and as soon as possible after the CO2 challenge. Throughout the procedure, vital signs such as blood pressure and heart rate will be continuously monitored. Lastly, biomarkers for neuroendocrine autonomic nervous system activation (plasma ACTH, cortisol and prolactin; saliva alpha-amylase and cortisol) and plasma orexin-1 will be assessed.

Study burden and risks

The CO2 challenge has previously been established as a safe and effective method to investigate panicogenic effects in healthy volunteers by multiple research groups. No serious adverse events have been reported, nor has there been evidence of increased risk of developing panic disorder (PD) as a result of these tests. Therefore, the potential CO2-related carry-over effects are non-existent.

The robust fear-like behavior CO2 induces in preclinical models mirrors the respiratory and cardiovascular effects observed in humans, making acute CO2 inhalation a valid translational fear challenge. The physiological nature of CO2 allows for real-time assessment of panic attacks (PAs) in experimental settings. This model also offers the possibility of demonstrating panicolytic effects of novel central nervous system (CNS) active compounds in human subjects. Multiple studies conducted at the Centre for Human Drug Research (CHDR) have indeed verified these panicolytic effects. In over 300 challenges with healthy volunteers at CHDR, the CO2 challenge was deemed safe with no serious adverse events.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy male or female aged between 18 and 65 years (inclusive) at screening who have been demonstrated to be sensitive to the panicogenic effects of the CO2 challenge in previous studies;
2. Sensitivity to the fear-inducing effects of 35% CO2 double-breath inhalation is defined as an increase from pre-CO2 to post-CO2 challenge in the following: PSL-IV total scores >=4 with at least 1-point increase for at least 4 of the symptoms specified in the PSL-IV and an increase on the Visual Analog Scale (VAS) Fear of at least 25 mm;
3. BMI of 18-32 kg/m2 (inclusive);
4. Non-smoker for at least 3 months.

Exclusion criteria

1. Subjects with a clinically significant current or past personal or family history of any psychiatric disorder as classified by DSM-4 or DSM-5 criteria.
2. Current or past history of alcohol or any substance abuse or dependence disorder within the past 12 months;
3. Clinically significant ECG abnormalities;
4. Clinically significant abnormality of the lungs (e.g. COPD, asthma, lung fibrosis) and hematologic diseases concerning hemoglobin (e.g. thalassemia and sickle cell disease);
5. Important cardiovascular history, or suspicion of infarct, cardiomyopathy, cardiac failure, TIA, angina pectoris, cardiac arrhythmias, CVA;
6. Personal or familial history of cerebral aneurysm.

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	26-10-2023
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	20-09-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	NL84999.056.23