ISRCTN13516283 https://doi.org/10.1186/ISRCTN13516283

Methodological optimization of the CO2 challenge

Submission date	Recruitment status	[_] Prospectively registered
12/02/2024	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[X] Statistical analysis plan
21/02/2024	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
21/02/2024	Mental and Behavioural Disorders	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Panic attacks (PAs) are episodes of intense fear characterized by feelings of dread, distorted thinking about potential threats, and physical symptoms due to the activation of the autonomic nervous system. They often occur suddenly and are assessed after the fact through questionnaires in research settings. However, this method has limitations, prompting the need for alternative ways to study PAs and test anxiety-reducing medications.

In the past, different methods like using certain substances or inducing hyperventilation were used to study PAs but were abandoned due to inconsistent results. Currently, inhaling carbon dioxide (CO2) is seen as a reliable method to trigger panic reactions similar to PAs both in how they feel and their physiological effects.

Research on this CO2 inhalation method has evolved since the 1980s. People with panic disorder (PD) are most sensitive to CO2, followed by their relatives and then healthy individuals. Anxiolytic drugs reduce CO2 sensitivity in both healthy people and patients over time.

Various CO2 inhalation protocols have been used, but differences in sensitivity among groups may be due to methodological variations. Standardizing these protocols is crucial for accurate comparisons between studies.

Studying the effects of single versus double breaths of 35% CO2 inhalation is important for validating this method. Our study aims to compare the two methods in healthy volunteers and assess the reliability of the CO2 challenge over time. Additionally, we'll investigate whether tolerance to CO2 develops in these volunteers, which hasn't been explored before in this population.

Understanding how healthy individuals respond to CO2 challenges and whether they become tolerant over time will inform future research and potentially lead to better testing methods for anxiety disorders.

Who can participate?
Healthy volunteers in the age range of 18 - 65 years

What does the study involve?
The total study duration will be 29 (+/-3) days, and subjects will undergo the CO2 inhalation challenge in total five times on Day 1, Day 8 (+/-3), Day 15 (+/-3), Day 22 (+/-3) and Day 29 (+/-3) of the study. No treatment will be administered.

What are the possible benefits and risks of participating?
The CO2 challenge has been widely recognized as a safe and effective way to study the effects of panic in healthy volunteers by multiple research teams. There have been no reports of serious side effects or evidence linking these tests to an increased risk of developing panic disorder. Therefore, concerns about any lasting effects from CO2 exposure are unfounded. The intense fear-like reactions induced by CO2 in animal studies closely resemble the respiratory and cardiovascular responses seen in humans, validating its use as a method to study panic in both animals and humans. This method allows researchers to assess panic attacks in real-time during experiments. It also provides an opportunity to evaluate the effectiveness of new compounds that affect the central nervous system in reducing panic symptoms in human subjects.

Studies conducted at the Centre for Human Drug Research (CHDR) have confirmed the effectiveness of this approach in identifying compounds with different mechanisms of action that can alleviate panic symptoms in CO2-sensitive healthy volunteers, demonstrating the reliability of the CO2 experimental model.

While over 300 challenges with healthy volunteers at CHDR have shown the CO2 challenge to be safe with no serious adverse events, some limitations have been identified that require further investigation to improve its use in phase 1 clinical trials. It's unclear whether a single breath or double breath of CO2 inhalation produces similar panic-inducing effects. Additionally, tolerance to the CO2 challenge may develop after repeated exposures in individuals sensitive to its effects, and it's unknown whether the reliability of the test over time extends to longer periods, possibly years.

Addressing these methodological concerns is crucial for two main reasons. Firstly, it will improve the reliability of the CO2 challenge model for future studies, potentially avoiding unnecessary exposure of individuals to the CO2 challenge in trials. Secondly, resolving these uncertainties may help minimize the burden on participants undergoing the CO2 challenge, ensuring their safety and well-being throughout the research process.

Where is the study run from?
The Centre for Human Drug Research, Leiden, the Netherlands

When is the study starting and how long is it expected to run for?
September 2023 to December 2023

Who is funding the study?
The Centre for Human Drug Research, Leiden, the Netherlands

Who is the main contact?
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Additional identifiers

Protocol serial number
CHDR2344

Study information

Scientific Title
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

Study objectives
In the past, various CO2 regimens have been applied to induce 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 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.

Panic attacks, characterized by sudden episodes of fear and discomfort, are challenging to study due to their unpredictable nature. The present methods, which rely on patient and clinician-rated questionnaires, have their limitations, thus sparking a need for more accurate alternative research methodologies.

In pursuit of better ways to understand and study panic attacks, a promising tool has been found: the intrapulmonary administration of carbon dioxide (CO2). This method has shown its ability to provoke panic reactions similar to those seen in spontaneous panic attacks. While past approaches involving substances like lactate and yohimbine or techniques like self-induced hyperventilation have been inconsistent and largely abandoned, the CO2 inhalation method has proven to be reliable and has undergone significant validation and refinement since the 1980s.

This model shows that people with panic disorder (PD), their first-degree relatives, and healthy volunteers each have decreasing levels of sensitivity to CO2. Moreover, anxiolytic drugs seem to decrease this sensitivity over time.

However, the results across different research groups vary due to differing CO2 administration protocols. The lack of a standardized CO2 testing procedure complicates matters, preventing accurate comparisons between studies. To address this, we are set to investigate the effectiveness of single and double 35% CO2 inhalations in inducing panic attacks in healthy volunteers.

Moreover, there's a gap in our understanding of the test-retest reliability of the CO2 inhalation challenge in the long term. While previous studies have investigated the reliability over short intervals, questions remain about whether sensitivity to CO2 can persist for years.

Lastly, an important area of investigation is the potential for tolerance or desensitization to the CO2 challenge in healthy volunteers who have shown previous sensitivity to it. While such studies have been conducted in panic disorder patients, the same hasn't been done in healthy individuals

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/09/2023, Stichting Beoordeling Ethiek Biomedisch Onderzoek (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31592405871; Info@stbebo.nl), ref: 056

Primary study design
Observational

Study design
Observational case crossover study

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Panic disorder, anxiety disorder

Interventions
Subject Recruitment and Study Procedure Overview
Participants are identified through a search in our internal database and contacted via email, which includes a brief overview of the study. Interested individuals are asked to express their interest by responding to the email. Subsequently, these participants receive a call from the study physician, who provides a detailed briefing about the study. They are then invited to a screening session on the first day of the study.
Following a successful screening, participants are scheduled for the first of five CO2 challenges, spaced approximately one week apart. The initial two CO2 challenges involve a randomized crossover between single and double inhalations. The remaining three sessions consist exclusively of double CO2 inhalations.

Measurements and Data Collection
During each CO2 challenge, we collect baseline data, including subjective measures (VAS for fear and discomfort, STAI Y1, and PSL) and objective measures (salivary cortisol and alpha-amylase, and serum cortisol, ACTH, orexin-1, and prolactin). These measurements are repeated post-challenge, with serum and saliva samples collected multiple times.
In the first session, participants also complete personality questionnaires (TCI, DPQ, and STAI Y2). After completing all five CO2 challenges, which are approximately one week apart, participants conclude their involvement in the study. There is no follow-up, making the total duration of participation around four weeks.

Intervention Type
Behavioural

Primary outcome(s)

Measured at Day 1, and subsequent sessions approximately one week apart (Day 8, Day 15, Day 22, and Day 29, with a 3-day margin of flexibility)
1. Fear measured using Panic Symptom List
2. Discomfort measured using Visual Analogue Scales

Key secondary outcome(s)
Measured at Day 1, and subsequent sessions approximately one week apart (Day 8, Day 15, Day 22, and Day 29, with a 3-day margin of flexibility):
1. State-Trait Anxiety Inventory Y1
2. Saliva cortisol
3. Saliva alpha-amylase
4. Serum cortisol
5. ACTH
6. Prolactin

Specific collection times for the biochemical markers in plasma (serum cortisol, ACTH, prolactin, and orexin-1) are strategically scheduled around each CO2 challenge at five intervals: a pre-challenge sample 15 minutes before, a sample within the immediate 5-minute window preceding the challenge, one directly in the 5-minute period following the challenge, and additional samples at 15-, 30-, 60-, and 120-minutes post-challenge.
Similarly, saliva samples for cortisol and alpha-amylase levels are methodically obtained at defined times around the CO2 challenge: one sample 10 minutes prior to the challenge, another within the 1-minute period just before the challenge, a third within the 1-minute period immediately after the challenge, and subsequent samples at 10, 20, 40, and 60 minutes after the challenge.

Personality assessments administered only once at the beginning of the study on Day 1:
7. Temperament and Character Inventory (TCI)
8. Dutch Personality Questionnaire (DPQ),
9. State-Trait Anxiety Inventory Y2,

Completion date
31/12/2023

Eligibility

Key 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.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
20

Key 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.

Date of first enrolment
10/10/2023

Date of final enrolment
30/10/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
The Centre for Human Drug Research
Zernikedreef 8
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Sponsor information

Organisation
Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
1. Data Description: The plan includes anonymized participant data such as demographics, CO2 sensitivity, panic response scores, and physiological data, provided in a machine-readable format.
2. Availability: Data will be made available by the end of Q3 2024, approximately 9 months post-study completion.
3. Platform: The data will be hosted on a scientific repository, which is yet to be determined, ensuring secure and long-term accessibility.
4. Documentation: The plan will include a data dictionary and metadata, along with a user guide to assist in the understanding and utilization of the data.
5. Preservation: The data will be preserved for 20 years post-study completion.
6. Compliance: The sharing of data will be in compliance with GDPR and other relevant data protection regulations, ensuring the privacy and confidentiality of participants are maintained, and the data is fully anonymized.
7. Contact: A. Safai Pour will be available for queries related to data access and use.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1	12/09/2023	21/02/2024	No	No
Statistical Analysis Plan	section 8 contains SAP version 1	12/09/2023	21/02/2024	No	No