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The CO2 study: Carbon dioxide insufflation and brain protection during open-heart surgery

Submission date	**Recruitment status**	[X] Prospectively registered
11/05/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/07/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
22/10/2025	Surgery	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Brain injury is a common complication after heart surgery. It affects about 6 in every 10 people who undergo open heart surgery. The injury can be severe, for example stroke, although this is rare. In most people the injury is milder, manifesting as problems with memory and thinking. In some patients, these problems can persist for up to one year after heart surgery and may increase the risk of developing dementia. Surgeons believe that brain injury results from microscopic air bubbles (microemboli) that enter the bloodstream when the heart is opened during surgery. These air bubbles are carried to the brain where they can get stuck in the small blood vessels and prevent blood from reaching that area of the brain, damaging, and eventually killing, surrounding nerve cells. One way that surgeons think they can reduce the number of air bubbles entering the bloodstream is by gently blowing the gas carbon dioxide into the area they are operating on. Carbon dioxide dissolves in blood much more easily than air, so it can displace air bubbles. However, there is little evidence that this technique, known as carbon dioxide insufflation (CDI), prevents brain injury after cardiac surgery. The CO2 study will test the hypothesis that CDI prevents brain injury in patients undergoing heart surgery.

Who can participate?

Adults aged ≥ 50 years with planned left side aortic or mitral valve surgical repair or replacement.

What does the study involve?

Patients who are undergoing surgery to repair or replace one or more of their heart valves will be randomised into two groups; one group will receive carbon dioxide gas blowing into the heart and the other group will receive medical air (placebo). Medical air has no effect on the amount of air entering the bloodstream. Neither surgeons nor participants will know which type of gas is being used; only the person operating the cylinder will know. Everything else about the operation will be exactly the same. Participants will have a very sensitive brain scan between 2 and 10 days after their surgery (diffusion weighted magnetic resonance imaging, or DW MRI). This is safe and should take no more than 30 minutes. Participants will also complete tests and questionnaires to assess brain and physical function and their quality of life before and 3 months after the operation. We will also collect information about how the operation went and any complications that the patients experience during and after the surgery, for example, strokes and kidney damage. We hope to recruit 704 patients from at least eight UK NHS cardiac surgery

centres into the trial. The trial is expected to take about 3 and half years to complete. We also want to do a small sub-study within the trial to determine whether CDI does lead to fewer air bubbles entering the circulation and whether fewer air bubbles means less damage to the brain. We will ask 100 patients taking part at the Bristol centre to have an ultrasound scan of the main artery going to their head during their operation. The ultrasound scan is safe and will not delay the operation. The scan will allow the number of air bubbles entering the blood stream to be counted using a computer. This information can be reviewed against the brain scan to see if patients with fewer bubbles have fewer areas of damage in their brains.

What are the possible benefits and risks of participating?
None

Where is the study run from?
Bristol Royal Infirmary (UK)

When is the study starting and how long is it expected to run for?
October 2019 to June 2026

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Lucy Hamilton, CO2-trial@bristol.ac.uk

Contact information

Type(s)
Public

Contact name
Ms Lucy Hamilton

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-001322-54

Integrated Research Application System (IRAS)
278171

Central Portfolio Management System (CPMS)
45760

Protocol serial number
CS/2018/6632

Study information

Scientific Title
Carbon dioxide insufflation and brain protection during open-heart surgery: a randomised controlled trial

Acronym
CO2

Study objectives
In patients undergoing open heart valve surgery via partial or full sternotomy, CDI plus standard de-airing is protective against ischaemic brain injury caused by cerebral embolisation (air microemboli) compared with medical air insufflation (placebo) plus standard de-airing.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/06/2020, East Midlands and Nottingham 2 REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8103; nottingham2.rec@hra.nhs.uk), ref: 20/EM/0130

Primary study design
Interventional

Study design
Multicentre placebo-controlled randomized controlled clinical trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Brain injury following open-heart valve surgery

Interventions
Participants will be randomised in a 1:1 ratio (stratified by type or procedure and centre) to receive either carbon dioxide insufflation (IMP) or medical air insufflation (placebo). Insufflation with the allocated intervention will be delivered at a flow rate of 5L/min from just before cannulation for cardiopulmonary bypass until 10 minutes after cardiopulmonary bypass. Participants will be followed up until they are discharged and again at 3 months.

Intervention Type
Device

Phase
Phase III

Drug/device/biological/vaccine name(s)
Not applicable

Primary outcome(s)
Acute ischemic brain injury within 10 days post-surgery based on new brain lesions identified with DW MRI or clinical evidence of permanent brain injury according to the updated definition of stroke for the 21st century

Key secondary outcome(s)
1. Number and volume of DWI brain lesions measured using the DW MRI conducted for each participant between 2-10 days post-surgery
2. Objective quantification of the impairment caused by new ischemic brain injury assessed using the National Institutes of Health Stroke Scale at pre-surgery, day 3 and three months post-surgery
3. Delirium assessed using the 3-minute diagnostic interview for Confusion Assessment Method at pre-surgery, day 3 and three months post-surgery
4. Functional status assessed using the Barthel Index score at pre-surgery and three months post-surgery
5. Neurocognitive function assessed at pre-surgery and three months post-surgery using the following tests:
5.1. Addenbrooke’s Cognitive Examination III
5.2. Trail making Tests A and B
6. Quality of life assessed using the 12-Item Short-Form Health Survey (SF-12) at pre-surgery and three months post-surgery
7. Composite of all-cause mortality, clinical stroke, or acute kidney injury within 30 days of surgery, by review of participants medical notes
8. Serious adverse events (SAEs) to 3 months, by review of participants medical notes and discussion with the participant at the three month post-surgery follow up visit
9. Survival to 3 months by review of the participants medical notes and attendance at the three-month post-surgery follow up visit

Completion date
30/06/2026

Eligibility

Key inclusion criteria
1. Age ≥ 50 years
2. Planned left side aortic or mitral valve surgical repair or replacement (with or without another procedure, e.g. coronary artery bypass graft) via a partial or full sternotomy using central aortic perfusion cannulae

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
50 Years

Sex
All

Key exclusion criteria
1. Contraindication to medical carbon dioxide: acquired or genetic of acidosis (i.e. renal tubular acidosis)
2. Contraindication to MRI (e.g. known intolerance, permanent pacemaker in situ or expected implantation of a permanent pacemaker)
3. History of clinical stroke within 3 months prior to randomisation
4. Cardiac catheterisation within 3 days of the planned surgery
5. Cerebral and/or aortic arch arteriography or interventions within 3 days of the planned surgery
6. Active endocarditis at time of randomisation
7. Planned concomitant aortic procedure such as root replacement
8. Clinical signs of cardiogenic shock or treatment with IV inotropic therapy prior to randomisation
9. Participation in an interventional (drug or device) trial
10. Unable to provide written informed consent
11. Prisoners

Date of first enrolment
06/10/2021

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Bristol Royal Infirmary
University Hospitals Bristol and Weston NHS Foundation Trust
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre

John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
University Hospital Southampton
Southampton University Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Castle Hill Hospital
Hull University Teaching Hospitals NHS Trust
Castle Road
Cottingham

United Kingdom
HU16 5JQ

Study participating centre
Victoria Hospital (blackpool)
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
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SW3 6NP

Sponsor information

Organisation
University Hospitals Bristol NHS Foundation Trust

ROR
https://ror.org/04nm1cv11

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available upon request from the sponsor, after publication of the main result of the study. Thereafter, anonymised data will be made available for secondary research, conditional on assurance the proposed use of the data is compliant with MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/05/2023	18/05/2023	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes