Carbon dioxide flooding to reduce postoperative neurological injury following surgery for acute type A aortic dissection: a prospective, randomised, blinded, controlled clinical trial, CARTA study protocol - objectives and design

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ABSTRACT
Introduction Neurological complications after surgery for acute type A aortic dissection (ATAAD) increase patient morbidity and mortality. Carbon dioxide flooding is commonly used in open-heart surgery to reduce the risk of air embolism and neurological impairment, but it has not been evaluated in the setting of ATAAD surgery. This report describes the objectives and design of the CARTA trial, investigating whether carbon dioxide flooding reduces neurological injury following surgery for ATAAD.

Methods and analysis The CARTA trial is a single-centre, prospective, randomised, blinded, controlled clinical trial of ATAAD surgery with carbon dioxide flooding of the surgical field. Eighty consecutive patients undergoing repair of ATAAD, and who do not have previous neurological injuries or ongoing neurological symptoms, will be randomised (1:1) to either receive carbon dioxide flooding of the surgical field or not. Routine repair will be performed regardless of the intervention. The primary endpoints are size and number of ischaemic lesions on brain MRI performed after surgery. Secondary endpoints are clinical neurological deficit according to the National Institutes of Health Stroke Scale, level of consciousness using the Glasgow Coma Scale motor score, brain injury markers in blood after surgery, neurological function according to the modified Rankin Scale and postoperative recovery 3 months after surgery.

Ethics and dissemination Ethical approval has been granted by the Swedish Ethical Review Agency for this study. Results will be disseminated through peer-reviewed media.

Trial registration number NCT04962646.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ A variety of neurological assessment methods will be used to assess the potential benefits of carbon dioxide flooding on neurological impairment following acute type A aortic dissection repair.
⇒ The CARTA trial is a single-centre study, which limits the number of study participants, reduces the generalisability of study results and influences the rate of participant recruitment.
⇒ Due to the urgent nature of the diagnosis, a thorough preoperative neurological assessment performed by a neurologist or MRI are not routinely performed, and therefore preoperative neurological injury may influence postoperative findings.
⇒ The study is performed by a dedicated research group which enables a randomised trial to be performed in a group of patients which is generally difficult to study.
⇒ The findings of this study may not be generalisable to the effects of carbon dioxide delivered by other devices than the TEMED device and with higher CO2 flows.

INTRODUCTION
Background and rationale Aortic dissection is a life-threatening condition caused by a tear of the tunica intima, the innermost layer of the aorta. The tear enables blood to dissect between the intima and the media creating a ‘false lumen’, which can obstruct branch artery vascular outflows with consequent organ ischaemia. The tear and the subsequent weakening of the aortic wall also increases the risk of rupture.

Acute type A aortic dissection (ATAAD) affects the ascending aorta, and up to half of all patients with ATAAD do not make it to the hospital, mainly due to aortic rupture resulting in lethal cardiac tamponade or exsanguination.1-3 Life-saving emergency surgery is required and routinely performed...
on ATAAD patients. Nonetheless, despite timely intervention, the 30 day mortality is 15%–20%.6–8 Neurological injury is one of the most feared complications related to elective as well as emergent aortic surgery. For instance, postoperative stroke has been reported in 5%–20% of patients undergoing elective aortic surgery depending on the extent of the procedure.9–10 In the setting of ATAAD surgery, 12%–15% of patients present with preoperative symptoms of cerebral malperfusion and large, multicentre studies have reported that 10%–16% of patients suffer postoperative stroke and 3%–9% of patients are rendered comatose after ATAAD surgery.11–15 In addition, our group has previously reported that neurological complications account for 15% of in-hospital mortality after ATAAD repair. Therefore, further efforts are necessary to reduce neurological impairment following ATAAD surgery.16 Several mechanisms may be responsible for brain injuries after ATAAD. First, cerebral malperfusion can be caused by embolisation, dissection of the carotid arteries or systemic hypotension, and patients with cerebral malperfusion have a twofold increase of postoperative neurological injury compared with patients without preoperative cerebral malperfusion.14–15 Second, the surgical procedure itself may contribute to neurological injury as all surgery for ATAAD relies on the use of cardiopulmonary bypass, and the location of arterial cannulation may influence perioperative haemodynamics and the risk of perioperative stroke.17 Furthermore, surgery for ATAAD is mainly performed under deep or moderate hypothermia with circulatory arrest (DHCA). A short period of circulatory arrest has been considered neurologically safe for most patients, but a recent meta-analysis showed that retrograde cerebral perfusion (RCP) during circulatory arrest is associated with lower rates of stroke and mortality compared with straight circulatory arrest, suggesting that even short periods of circulatory arrest may contribute to cerebral injuries.17–18

Most ATAAD surgery is performed with an open distal anastomosis, permitting significant volumes of air to enter the arterial system. Once the circulation is reinstigated, air trapped within the aorta has the potential of causing air embolization to peripheral organs, including the brain. One way of reducing this risk is by displacing air from the surgical field by means of carbon dioxide flooding. Carbon dioxide has 1.5 times the density of air, is 25 times more soluble in blood and may thereby reduce the risk of air embolism.19 Carbon dioxide flooding is often used in open left-heart surgery, especially in minimally invasive procedures, and has been shown to improve segmental wall motion of the heart and reduce neurological impairment and levels of biomarkers for neurological injury.20–23 Although there are no documented risks associated with carbon dioxide flooding, it is not routinely employed, and no studies have evaluated the potential benefits of carbon dioxide flooding during ATAAD repair.

**Objective**

We hypothesise that air embolisation is a significant source of neurological injury associated with ATAAD repair. Our objective is to assess whether carbon dioxide flooding may reduce neurological injury following ATAAD surgery.

**Trial design**

The carbon dioxide flooding for reduction of neurological injury following surgery for ATAAD (CARTA) trial is a prospective, randomised, blinded, single-centre, controlled study.

**METHODS**

**Study setting**

The study will take place at the department of cardiothoracic surgery at Skåne University Hospital, Lund, Sweden. This is a tertiary care centre with an annual case load of approximately 30 ATAAD procedures. Inclusion of patients started on 1 January 2022.

**Eligibility criteria**

All patients over the age of 18, presenting with an ATAAD with symptom duration <14 days who are offered open-heart surgery will be screened for inclusion. Exclusion criteria include previous open-heart surgery, new onset neurological symptoms at the time of inclusion, prior stroke with persisting disability, surgery performed with cross clamping of the aorta without open distal anastomosis or open inspection of the distal aorta, presence of implants or devices not compatible with MRI or if the patient or next of kin declines study participation. Preoperative neurological symptoms are defined as either focal neurological symptoms or coma defined as Glasgow Coma Scale motor score (GCS-M)<6.24

**Recruitment**

All patients accepted for ATAAD surgery at our centre will be screened preoperatively for eligibility by the attending surgeon. Any uncertainties regarding the eligibility criteria related to preoperative neurological function are discussed with an attending neurologist.

**Intervention**

Patients will be randomised to surgical field flooding using carbon dioxide at a flow of 5 L/min using a CO₂ diffuser (TEMED Gasdiffuser, HMT, Germany) from the opening of the chest until the closure of the aorta, or no CO₂ flooding. A flow of 5 L/min of carbon dioxide is routinely used at our institution. When used, CO₂ flooding is started as soon as the chest is opened and since all our aortic dissection repairs are performed during deep hypothermic circulatory arrest, the time from the chest is opened until circulatory arrest is at least 30 min, which should provide sufficient time to fill the pericardium and any open pleural space with CO₂. Except for the intervention, surgery is performed following local standard. General anaesthesia is commonly induced with propofol, fentanyl and rocuronium bromide and maintained with...
propofol and remifentanil. Surgery is performed with median sternotomy, cardiopulmonary bypass and intermittent cold blood cardioplegic cardiac arrest. Arterial cannulation site varies by patient and surgeon but commonly femoral artery or direct aortic cannulation is employed, aided by guidewire and transesophageal echocardiography, ensuring access to the true lumen. Venous access is achieved through either bicaval cannulation or two-stage atrial cannula. Before the circulation is stopped, our neuroprotection strategy includes topical cooling of the head and administration of thiopental (1 g) and hydrocortisone (500 mg). An open distal anastomosis is performed under deep hypothermic circulatory arrest (<22°C) without prior use of aortic cross clamp. During cooling and circulatory arrest, arterial blood gas analyses are interpreted using the pH-stat method, and the alpha-stat strategy is used during rewarming. The target pCO₂ is 5.5 kPa at a core temperature of 37°C and body temperature is measured using urinary bladder measurement. Target blood glucose levels are 6–10 mmol/L and managed according to department standard using intravenously administered insulin. In selected patients, selective antegrade cerebral perfusion (ACP) or RCP may be used. After circulatory arrest, perfusion is restarted using a side-branch of the vascular prosthesis when the patient is in a Trendelenburg position which enables deairing before the vascular graft is clamped. Root and aortic valve procedures, in cases when this is required, and suturing of the proximal anastomosis is performed during rewarming.

Outcomes

The primary outcomes of this study are number and volume of ischaemic lesions observed using diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences on MRI after the surgery (Box 1). The secondary outcomes are clinical signs of neurological injury after surgery, levels of established blood-based biomarkers for neurological injury, that is, S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), neurofilament light polypeptide (NFL), glial fibrillar acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) and total-Tau (t-Tau) after surgery, as well as postoperative recovery and neurological function 3 months postoperatively. Subgroup analyses of the primary outcomes and levels of biomarkers will be performed in regard to the use of RCP.

Participant timeline

The participant timeline is presented in Figure 1.

Sample size

To date, there are no studies to indicate the effect of carbon dioxide flooding on postoperative neurological outcomes following ATAAD surgery. However, Leshnower et al published a study showing that RCP in conjunction with aortic surgery reduces the occurrence of ischaemic lesions from 100% to 45% and the number of these lesions

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Summary of study endpoints</th>
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<tr>
<td><strong>Primary outcomes</strong></td>
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<tr>
<td>⇒ Number of ischaemic lesions on MRI performed before postoperative day 7 unless impossible due to medical considerations, otherwise performed as soon as possible.</td>
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<tr>
<td>⇒ Volume of ischaemic lesions on MRI performed before postoperative day 7 unless impossible due to medical considerations, otherwise performed as soon as possible.</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>⇒ Clinical neurological injury (Coma according to clinical neurological assessment and/or clinical focal neurological injuries assessed by neurologist or verified ischaemic lesions on MRI).</td>
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<tr>
<td>⇒ Neurological function (NIHSS). Assessed on postoperative day 4 or when leaving the ICU and at 3 months after surgery. Minimum score 0 points, maximum score 42 points, with 42 points being the worst outcome.</td>
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<tr>
<td>⇒ Neurological function (mRS). Assessed on postoperative day 4 or when leaving the ICU and at 3 months after surgery. Minimum score 0 points, maximum score 6 points, with 6 points being the worst outcome.</td>
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<tr>
<td>⇒ Level of consciousness (GCS-M). Assessed on postoperative day 4 or when leaving the ICU and at 3 months after surgery. Minimum score 1 point, maximum score 6 points, with 6 points being the best outcome.</td>
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<tr>
<td>⇒ Levels of S100B (serum concentration of S100B at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Levels of NSE (serum concentration of NSE at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Levels of NFL (plasma concentration of NFL at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Levels of GFAP (plasma concentration of GFAP at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Levels of UCH-L1 (plasma concentration of UCH-L1 at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Levels of Tau (plasma concentration of t-Tau at predefined time points: preoperatively, 24 hours after the start of the procedure, postoperative day 4 and 3 months after surgery.)</td>
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<tr>
<td>⇒ Neurocognitive function (MoCA test). Assessed at 3 months after surgery. Minimum score 0 points, maximum score 30 points, with 30 points being the best outcome.</td>
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<tr>
<td>⇒ Neurocognitive function (SDMT). Assessed at 3 months after surgery. Minimum score 0 points, maximum score 30 points, with 30 points being the best outcome.</td>
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<tr>
<td>⇒ Postoperative recovery (postoperative recovery profile). Assessed at 3 months after surgery. Minimum score 19 points, maximum score 76 points, with 76 points being the best outcome.</td>
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<tr>
<td>⇒ Quality of life (satisfaction with life scale). Assessed at 3 months after surgery. Minimum score 0 points, maximum score 35 points, with 35 points being the best outcome.</td>
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<tr>
<td>⇒ Quality of life (EQ-5D-5L). Assessed at 3 months after surgery. Minimum score 0 points, maximum score 25 points, with 25 points being the best outcome.</td>
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<tr>
<td>⇒ Neurological recovery (two simple questions for stroke) Assessed at 3 months after surgery. Minimum score 0 points, maximum score 2 points, with 2 points being the worst outcome</td>
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| EQ-5D-5L, EuroQol 5 dimensions 5 levels; GCS-M, Glasgow Coma Scale motor score; GFAP, glial fibrillar acidic protein; MoCA, Montreal Cognitive

Continued
by 70% compared with ACP.25 Previous studies have shown that 61% of patients who underwent routine aortic valve replacement have postoperative ischaemic lesions visualised by MRI.26 We hypothesise that the beneficial effect of RCP showed by Leshnower et al is due to a reduction of air embolism and we, therefore, used this data as a basis for our power calculation. The results of Leshnower et al suggest a reduction in the number of ischaemic lesions from 4.0±3.5 to 1.2±2.1. A study sample of 25 patients in each arm would yield 80% power to detect a significant difference between the groups with a 0.05 significance level (alpha). A 50% reduction of ischaemic lesions from a baseline prevalence of 70% (as in the study by Leshnower and colleagues) would require 31 patients in each arm to achieve similar statistical power. We presume loss of follow-up due to 5%–10% mortality during or immediately after the surgical procedure, and, therefore, we aim to include 40 study patients in each arm. With an annual case load of 30 ATAAD patients at our institution, we expect an inclusion period over 3 years.

### Allocation

This is a prospective, randomised study to compare an intervention group with a non-intervention group (control subjects). Accordingly, we performed a 1:1 randomisation of 80 participants using block randomisation with blocks of variable size. The randomisation has been performed by external consultants (Clinical Studies Sweden, Forum South), and consecutively numbered envelopes are attached to each Case Report Form.

Figure 1 Flow chart for inclusion and assessment of study participants in the CARTA trial. GCS-M, Glasgow Coma Scale motor score; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale for neurologic disability; NFL, neurofilament light polypeptide; NIHSS, National Institutes of Health Stroke Scale; NSE, neuron-specific enolase; S100B, S100 calcium-binding protein B; SDMT, Symbol Digit Modalities Test; t-Tau, total-Tau; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.
Blinding
Carbon dioxide changes the colour of the blood pooled in the surgical field, which makes it impossible to achieve blinding for the surgical team. Study investigators may be scrubbed in or collecting data during these procedures making it difficult to strictly blind the intervention for them. Patients and the outcome assessors will be blinded for the randomisation. The clinical assessment on post-operative day 4 and 3 months after surgery will not be conducted by an individual present during the operation.

Data collection method

MRI assessment
Brain MRI will be carried out as soon as the external pacemaker wires have been removed, if possible, within the first 7 days of surgery. Daily assessment of the need for external pacemaker will be conducted from postoperative day 3. If pacemaker wires cannot be removed by postoperative day 7, the imaging will be carried out as soon as the wires are removed. A standard protocol is used with DWI-MRI and FLAIR images with slice thickness of 4 mm and all lesions seen on DWI and apparent diffusion coefficient maps will be considered positive and counted in the number of ischaemic lesions.

A neuroradiologist blinded to the randomisation and the clinical outcomes following surgery will analyse the images and quantify the number and volume of ischaemic lesions. Furthermore, the lesions will be described as focal (related to embolism) or watershed (related to hypoperfusion) and according to their anatomical locations.

Biomarkers
A sample volume of 10 mL of blood will be collected before surgery, 24 hours after the start of surgery, 4 days after surgery and 3 months after the procedure. S100B and NSE will be analysed immediately using electrochemiluminescence immunoassays, while NFL, GFAP, UCH-L1 and t-Tau will be analysed using the Simoa 4-plex analysis kit in one batch after the completion of the trial. These samples will be centrifuged at 2000 g for 10 min and stored in a biobank until batch analysis is performed.

Neurological assessment
Patients will be assessed using the National Institutes of Health Stroke Scale (NIHSS), the modified Rankin Scale for neurologic disability (mRS) and the GCS-M 4 days after surgery.27,28 The neurological assessment will be conducted by physicians with certified completion of the NIH Stroke Scale Training Programme (https://learn.heart.org). If still on ventilator on the fourth postoperative day, the assessment will be performed once the patient is extubated and not under the influence of sedatives. The occurrence of clinical postoperative stroke will be defined as the presence of focal neurological symptoms persisting for more than 24 hours confirmed by a neurologist and a postoperative MRI. A transient ischaemic attack is defined as a transient episode of focal neurological symptoms that resolve within 24 hours regardless of radiological findings. Three months after surgery, patients’ neurological function will be re-evaluated using the NIHSS, mRS, Montreal Cognitive Assessment (MoCA) test, Symbol Digit Modalities Test (SDMT) and 2 Simple Questions for Stroke.29–31 Postoperative recovery and quality of life will be assessed using the Postoperative Recovery Profile, the Satisfaction with Life Scale and EuroQol 5 dimensions 5 levels (EQ-5D-5L).32–34

Statistical methods
Baseline data, variations in surgical management and specific techniques used will be described as appropriate. Groups will be compared using independent sample t-test and Mann-Whitney U-test depending on distribution of the data. Chi-squared test will be used for categorical data or Fisher’s exact test in samples with fewer than five observations. Subgroup analyses will be performed comparing patients operated using RCP versus those undergoing surgery under straight hypothermic circulatory arrest.

Data monitoring and harms
A data monitoring committee will not be established for this study due to there being no data to suggest that carbon dioxide flooding poses any medical risks for the patient receiving the intervention. Instead, an interim analysis will be performed after 40 patients have been randomised. An external statistician will analyse the primary outcomes and safety parameters including intraoperative mortality, in-hospital mortality, myocardial infarction, stroke and other thromboembolic events (table 1). Based on these analyses and the recommendation of the external statistician, the study investigators may at this point decide to terminate the study due to futility, superiority or harm. The principal investigator will consolidate data acquired by individual researchers and thus be the only person with access to the entire data set.

Patient and public involvement
There were no patient or public involvement when designing this study.

ETHICS AND DISSEMINATION
Ethical approval for this study has been granted by the Swedish Ethical Review Agency (ref: 2021-02039, date: 5 May 2021). In stable patients where this is possible, a written, informed consent will be collected. When the urgent nature of the diagnosis or the patients’ condition does not allow for a written consent to be obtained, an oral consent will be obtained from next of kin and in cases where the patient regains adequate cognitive abilities, written informed consent will be collected postoperatively. The consent will be obtained by the study investigators. The study participants can opt out from the study at any time and collected samples will be destroyed if so requested. All study-related information will be stored in locked file cabinets, while electronic databases will be password protected. Coded identification numbers will
be used to conceal personal information on all laboratory specimens and data collection forms.

Results will be disseminated in peer-reviewed journal using the Consolidated Standards of Reporting Trials statement recommendations. For the protocol Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines was used.35

Data availability statement
All results data of this study will be provided in the manuscript and supplementary files. Participants’ study information will not be released outside of the study, except as necessary for monitoring.

DISCUSSION
This paper describes the protocol of an ongoing prospective, randomised, blinded, controlled, single-centre study, with the aim to assess whether the flooding of carbon dioxide in the surgical field may reduce postoperative neurological injury in patients undergoing ATAAD surgery. The rationale of this study is our hypothesis that a significant proportion of neurological injury after ATAAD surgery occurs secondary to intraoperative air embolism. Previously, Massaro et al demonstrated that 61% of all patients undergoing surgical aortic valve replacement due to aortic valve stenosis show signs of acute brain infarction on MRI despite the extensive decalcification of the aortic annulus being performed in association with these procedures.26

Adding to the notion that air embolism is one of the mechanisms causing cerebral injury following ATAAD surgery, Leshnower et al showed that patients undergoing elective arch surgery with RCP and DHCA had fewer MRI lesions than those undergoing surgery with ACP and moderate hypothermic circulatory arrest (45% vs 100%).25 Furthermore, in a large meta-analysis, Tian et al demonstrated improved outcomes in terms of lower rates of mortality and stroke in elective arch surgery with RCP+DHCA versus DHCA alone.18 As it has been shown that RCP has little to no positive effect on brain metabolism, it can be speculated that the beneficial effect of RCP could come from topical cooling of the brain or from retrograde washout of embolic material.25 In patients undergoing ATAAD surgery, the presence of calcifications or other solid embolic material is usually very limited and, therefore, we hypothesise that a significant source of embolic lesions during the procedure is air trapped in the circulation during circulatory arrest.

Besides standard deairing procedures, carbon dioxide is used at some centres in left-sided heart surgery to displace

Table 1  Variable and outcome definitions of the CARTA trial

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<th>Definitions</th>
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<tr>
<td>Hypertension</td>
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<td>Chronic obstructive lung disease</td>
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<td>Diabetes mellitus</td>
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<td>Peripheral vascular disease</td>
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<td>Previous CVA</td>
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<td>Malperfusion</td>
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<td>Duration of operation</td>
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<td>Postoperative cardiac failure</td>
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<tr>
<td>Postoperative IABP, ECMO or Impella</td>
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<td>Postoperative myocardial infarction</td>
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<td>Postoperative atrial fibrillation</td>
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<td>Postoperative CVA</td>
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<td>Postoperative renal replacement therapy</td>
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<td>Reoperation for bleeding</td>
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<td>Index hospitalisation</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Transient ischaemic attack</td>
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<td>Coma</td>
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CRRT, continuous renal replacement therapy; CVA, cerebrovascular insult; ECMO, extracorporeal membrane oxygenation; GCS, Glasgow Coma Scale; IABP, intra-aortic balloon pump; RLS, reaction level scale.
air. Carbon dioxide has been shown to reduce microembolisms in patients undergoing valve surgery and reduce levels of S100B in blood after mitral valve surgery, which suggest a neuroprotective effect of carbon dioxide insufflation.\textsuperscript{29, 37} Although some centres use carbon dioxide routinely in ATAAD surgery, its potential benefit has not been scientifically established. In our opinion, this trial is well motivated as there is a lack of agreement regarding benefits of carbon dioxide treatment in ATAAD. If this study is able to show that carbon dioxide flooding has a beneficial effect on postoperative neurological outcomes, this could lead to wider implementation of carbon dioxide flooding in association with ATAAD repair as well as with other open left-heart surgery.

There are several limitations to this study. First, ATAAD is a lethal condition requiring immediate surgery. The urgent nature of the diagnosis does not allow for detailed preoperative neurological assessment and MRI, thus making it difficult to determine whether postoperative findings are the result of discrete or subclinical preoperative neurological injury. Furthermore, the surgical techniques employed, including cannulation and cerebral protection strategies, are at the discretion of each surgeon. This may introduce technical bias, especially as the surgeons are not blinded to the intervention arm. To address the potential for technical bias, however, the cannulation and cerebral protection strategies are determined prior to randomisation regardless of surgeon preference, and together with randomisation and reviewer blinding, we believe that we have minimised if not completely eliminated the effect of technical bias. In this study, we have used the TEMED gasdiffuser and a carbon dioxide flow of 5\text{L/min}, since this has been our institutional routine for many years. There is research available which shows that the use of alternative delivery devices and a flow of 10\text{L/min} may be more efficient for displacing all air within the surgical field, but despite this limitation, the strategy used at our institution is widely employed and still displaces more than 90% of air trapped in the surgical field.\textsuperscript{26-29} Furthermore, NSE values are influenced by the levels of free haemoglobin due to haemolysis caused by the inherent nature of the procedure. This may render any conclusions regarding the usefulness of NSE difficult, and therefore we have used several different biomarkers of cerebral injury. Another limitation of this study is the single-centre design. A multicentre study would have been preferable, allowing for a larger study cohort and possibly providing more generalisable results. However, ATAAD is a hyperacute condition. In the majority of cases, the patients are transferred directly to the operating room and during preparations for surgery, the study investigator needs to consult and obtain informed consent from next of kin, complete randomisation and collect the preoperative blood samples. Therefore, this study requires that the study investigator be available any time of day, 7 days a week. Although we have considered the possibility of a multicentre design, our experience from previous prospective trials in ATAAD patients is that the complexity of the study requires a highly dedicated team of investigators and a strictly controlled setting. Thus, we concluded that the downside of a reduced inclusion rate of study participants with a single-centre study is outweighed by superior protocol adherence, study supervision and better quality results. Also, the power calculation is based on previous research comparing RCP to ACP.\textsuperscript{25} These findings may not be translatable to this specific study and the occasional use of RCP in addition to CO\textsubscript{2} at our institution may introduce the risk of type II errors.

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Contributors JE, KT-H and IZ conceived the study. JE, KT-H, MM-K, BR, HB, PE, ML, NM-C, JS, PW, SN and IZ designed the trial. JE drafted the first version of the manuscript aided by KT-H, IZ and MM-K. All authors reviewed and revised the manuscript and approved the final version.

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Competing interests None declared.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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