

BMJ Open Feasibility of Improving Cerebral Autoregulation in Acute Intracerebral Haemorrhage (BREATHE-ICH) study: a protocol for an experimental interventional study

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ABSTRACT

Introduction Cerebral autoregulation (CA) is impaired in a multitude of neurological conditions. Increasingly, clinical studies are correlating the nature of this impairment with prognostic markers. In acute intracerebral haemorrhage (ICH), impairment of CA has been associated with worsening clinical outcomes including poorer Glasgow Coma Score and larger haematoma volume. Hypocapnia has been shown to improve CA despite concerns over hypoperfusion and consequent ischaemic risks, and it is therefore hypothesised that hypocapnia (via hyperventilation) in acute ICH may improve CA and consequently clinical outcome. BREATHE-ICH is a CA-targeted interventional study in acute ICH utilising a simple bedside hyperventilatory manoeuvre.

Methods and analysis Patients with acute ICH within 48 hours of onset will be included. The experimental set-up measures cerebral blood flow (cerebral blood velocity, transcranial Doppler), blood pressure (Finometer) and end tidal carbon dioxide (capnography) at baseline, and in response to hypocapnia (–5 mm and –10 mm Hg below baseline) achieved via a 90 s hyperventilatory manoeuvre. Autoregulation is evaluated with transfer function analysis and autoregulatory index calculations. Important classical endpoints associated with this before and after interventional study include death and disability at 14 days and the proportion of recruited individuals able to comply with the full measurement protocol.

Ethics and dissemination A favourable opinion was granted by the East Midlands-Nottingham 1 Research Ethics Committee (17/EM/0283). It is anticipated that the results of this study will be presented at national and international meetings, with reports being published in journals during late 2018.

Trial registration number NCT03324321.

INTRODUCTION

The ability to maintain an adequate brain-blood flow despite sudden changes in blood pressure (BP) can be measured in an individual and is referred to as the process of ‘autoregulation’.¹ This control process has been shown to be impaired in acute

Strengths and limitations of this study

- The study set-up carefully considers risks of hypoperfusion during the manoeuvre in a vulnerable clinical neurological circumstance.
- Although participants recruited to the study are likely to be mild to moderate stroke severity, as evidenced by neurological impairment (National Institutes of Health Stroke Scale 5–12) and Glasgow Coma Score >8 in similar experimental studies, this study is designed to assess feasibility and provide important mechanistic insights into the impact of a novel cerebral autoregulation (CA)-targeted intervention.
- The proposed study investigates for the first time whether a CA-targeted intervention involving a simple breathing exercise in survivors of acute intracerebral haemorrhage is safe, feasible and effective in improving CA and subsequently clinical outcomes.

ischaemic stroke (AIS), head injury, in dementia or following premature birth, but importantly is associated with worse patient outcomes.² An Autoregulation Index (ARI) can be assigned between 0 and 9 (0 being poor and 9 being the most efficient cerebral autoregulation (CA) observed) to gauge how good the control over cerebral blood flow (CBF) is at a given time.³ Dynamic CA (dCA) is a measure of the response of CBF to rapid changes in BP, and several key studies have shown impaired dCA postacute intracerebral haemorrhage (ICH).^{4–8} Recent studies have demonstrated that dCA impairment lasts up to 12 days,^{7 8} and that CA is bilaterally disturbed after supratentorial ICH.⁸ Importantly, the most recent study showed larger haematoma volume is likely to independently predict poorer CA status ipsilateral to haematoma.⁸

Spontaneous acute ICH is associated with both high mortality and morbidity.⁹ There

is a relative paucity of management options for acute ICH compared with AIS with BP control the foremost approach. However, controversy exists as to whether intensive BP lowering in acute ICH risks cerebral ischaemia. This is particularly the case if CBF control mechanisms are altered by chronic hypertension or indeed ICH itself. CA provides a protective mechanism for the brain parenchyma from extremes of CBF change, with the risk of hyperperfusion or hypoperfusion in response to systemic BP changes. A key limitation of large-scale randomised controlled trials has been the ability to provide mechanistic insight into CBF during the acute phase of haemorrhagic stroke.¹⁰ Lower mean CBF, in combination with impaired CA, may have implications for more intensive BP lowering and warrants further studies examining such strategies on CBF regulatory mechanisms.

Hypocapnia has been historically used in the management of acute brain injury to reduce intracranial pressure (ICP) and to improve outcome in specific circumstances.^{11 12} This is usually weighed against the risk of hypoperfusion and subsequent neuronal ischaemia, which could worsen outcome. Arterial carbon dioxide tension (PaCO₂) is a balance between production and removal.¹² In order to generate hypocapnia, this usually involves a hyperventilatory manoeuvre often in the intubated patient. The use of hypocapnia in acute brain injury has been primarily focused around the scientific principles of the Monro-Kellie doctrine describing the brain as a 'closed box' with a fixed volume.¹¹ Raised ICP (sustained >20 mm Hg) can cause secondary brain injury by impairing cerebral perfusion, direct pressure or by brainstem herniation.¹²

Hypocapnia can be induced to lower ICP by decreasing the CBF via cerebral arterial vasoconstriction. The effects can be potent: CBF decreases by approximately 3% per mm Hg change in PaCO₂ (range, 60–20 mm Hg PCO₂) in patients with traumatic brain injury (TBI).^{11 13} Despite advances in our understanding of PaCO₂ changes in TBI and other circumstances associated with raised ICP, little is understood about the use of hyperventilation in acute stroke. Hyperventilation has classically been advocated in acute stroke for two reasons: first to reduce ICP, and second to restore homeostasis to penumbral zones around ischaemic tissue by inducing inverse steal and correcting acidosis.¹² These physiological changes are weighed against both potential vasoconstriction leading to hypocapnia-induced brain ischaemia as well as cerebral hyperaemia due to subsequent normalisation of PaCO₂.¹² Lastly, cerebral ischaemic lesions noted on MRI in patients with acute ICH also raise the possibility of harms associated with BP lowering which may be more relevant than issues of perihaematoma ischaemia.

Hitherto, randomised studies have only been conducted in patients with TBI, with benefits noted in sustained ICP below 25 mm Hg, but with a less favourable outcome in those with moderate motor impairment on their Glasgow Coma Score (GCS).^{14 15} However, this population is very

different from acute stroke patient populations, which form the focus of this study.

This method of manipulating dCA may improve CA in acute ICH; offering a novel non-pharmacological intervention, particularly as hypocapnia (induced by hyperventilation), has been used as a neuroprotective mechanism improving impaired dCA in rats with subarachnoid haemorrhage,¹⁶ in patients with liver failure,¹⁷ and patients undergoing isoflurane anaesthesia¹⁸ and acute bacterial meningitis.¹⁹

Importantly, hypocapnia decreases CBF but expands the plateau region of the cerebral autoregulatory curve, hence improving CA and subsequently the ability to keep CBF constant for a wide range of perfusion pressures.^{20 21} Manning *et al* demonstrated systolic BP variability confers a poor outcome in acute ICH and concluded that peaks in systolic BP are likely to confer harm, as opposed to smooth and sustained early intensive lowering (to 140 mm Hg) which is likely to be beneficial.²² However, with a growing body of evidence highlighting impaired CA as a marker of poor prognostic outcomes in acute ICH, this relationship is likely to hold significant importance in possible alternative interventions for this devastating neurological state. The argument therefore for assessing the feasibility of hypocapnia for improving CA in acute ICH rests on mild to moderate hypocapnia possibly being of greater clinical benefit than methods that are designed to alter the magnitude of CBF. Therefore, the study will assess if: (1) ICH sufferers will tolerate the hyperventilation manoeuvre; (2) hyperventilation manoeuvre leads to hypocapnia in the ICH population; (3) dCA will be improved, while maintaining safe levels of CBF. The proposed study investigates for the first time whether a CA-targeted intervention involving a simple breathing exercise in survivors of acute ICH is safe, feasible and effective in improving CA and subsequently clinical outcomes. If successful we hope to take this simple bedside intervention forward to design a larger randomised controlled trial.

METHODS AND ANALYSIS

Sample selection

Patients with acute ICH, recruited within 48 hours of onset, able to comply with a respiratory manoeuvre (hyperventilation).

Each patient with stroke will be required to participate for up to 14 days poststroke symptom onset, during which up to a total of two assessments will be made. The first assessment will be recorded while the participant is an inpatient under the care of the University Hospitals of Leicester NHS Trust Stroke Service (acute: within 48 hours of symptom onset); the next assessment will be within 10–14 days poststroke onset (subacute).

The sample size included is based on the investigators' pilot study, which included 45 healthy volunteers who underwent the hyperventilation manoeuvre outlined in the 'Intervention' section (Minhas *et al*, unpublished data).

Formal sample size calculations have been previously conducted. In order to detect a change of 1 unit in ARI, and to calculate the required sample size we followed the technique as previously described by others.²³ For this study, a minimum sample of 40 patients provides 80% power at the 5% significance level to detect a difference in ARI of 1 unit.

The inclusion and exclusion criteria were determined based on the clear need for the recruited individual to be able to engage with the instructions associated with the manoeuvre to ensure as reliable a physiological measurement as possible.

Inclusion criteria

- ▶ clinical diagnosis of haemorrhagic stroke within 48 hours of onset (for patients waking with a stroke, time of onset will be taken to be the time when the patient was last asymptomatic);
- ▶ able and willing to give informed consent;
- ▶ male or female, aged 18 years or above;
- ▶ able (in the investigator's opinion) and willing to comply with all study requirements;
- ▶ willing to allow his or her general practitioner to be notified of participation in the study.

Exclusion criteria

- ▶ male or female, aged below 18 years;
- ▶ significant previous airway disease (formal diagnosis of moderate or severe airway disease and having treatment for this respiratory condition—via inhalers or specialist input);
- ▶ unable (in the investigator's opinion) or unwilling to comply with any study requirements;
- ▶ female participants who are pregnant, lactating or planning pregnancy during the course of the study;
- ▶ clinical diagnosis of stroke greater than 48 hours from onset;
- ▶ having had a resolved transient ischaemic attack (ie, neurological symptoms completely resolved upon hospital presentation);
- ▶ comorbidity with anticipated life expectancy less than 3 months.

Intervention

The level of impairment of dCA will be compared with extent of CT acute ICH findings. dCA measurements will be measured as below with a hyperventilation protocol. This will involve sustained periods of 90s of hyperventilation at two levels (-5 mm Hg and -10 mm Hg below baseline end tidal carbon dioxide (EtCO₂)) regulated using a metronome. The patients will receive a demonstration from the conducting physician clarifying the expected relationship of their breathing with the metronome beat. Two-minute washout periods of normal respiration will be allowed between successive measurements. Each incremental reduction in PCO₂ will be repeated on two occasions during the same session.

Participants will be monitored throughout the process and any unexpected physiological changes will be recorded on an adverse event form. These will be gathered and discussed on a monthly basis with a clinician independent from the study team within our institution (to replicate a data safety monitoring process). Furthermore, individuals will be compared with age-matched controls from the Leicester Cerebral Haemodynamics Database² and the pilot study to ensure physiological parameters are within acceptable limits (Minhas *et al*, unpublished data). Furthermore, in preparation for the study, lower limits of acceptable EtCO₂ (29 mm Hg) and cerebral blood velocity (CBV; 33 cm/s) will be calculated as within 1 SD from the mean hypocapnia level for cohort of healthy volunteer values and based on previous acceptable limits in TBI studies.²⁴ This will help protect individuals from risk of ischaemia associated with hypocapnia-induced vasoconstriction.

Interpretation

Important classical endpoints associated with this before and after interventional study include death and disability at 14 days (modified Rankin Scale) and the proportion of recruited individuals able to comply with the full measurement protocol. Furthermore, the data will be assessed for quality during the analysis protocol and rejected data files recorded with associated reasoning. Lastly, the percentage change in CBV at baseline and in response to a hypocapnic manoeuvre in the acute phase (<48 hours) and subacute phase (10–14 days) will be recorded alongside ARI. Importantly, this study is designed to test the feasibility of a CA-targeted intervention using hyperventilation. This inclusion of clinical outcomes is not necessarily the main objective of the study but highly relevant as an early indicator of feasibility to support design of robust larger trials. In conclusion, understanding the percentage of patients able to comply with the manoeuvre and whether preservation of autoregulation in this population is possible will provide a strong basis for future work.

Data collection and integration

For all subjects, all assessments will be undertaken in a dedicated cardiovascular research laboratory at Leicester Royal Infirmary, which is at a controlled temperature (20–24°C) and is free from distraction or on the hyperacute stroke ward using the mobile physiological measurement equipment (figure 1) if unable to transfer to the laboratory. The subject will lay supine on an examination couch. Baseline casual BP will be calculated as a mean of three supine brachial BP readings using a validated UA767 BP monitor. Beat-to-beat non-invasive BP will be recorded continuously using the Finometer cuff device attached to the middle finger of the non-dominant hand (non-hemiparetic hand in patients with stroke). R-R interval will be recorded using a 3-lead ECG. Respiratory rate will be recorded, and end tidal PCO₂ (EtCO₂) monitored using small nasal cannulae placed at the base of the nose (Salter Labs, ref 4000) attached to a capnograph (Capnograph

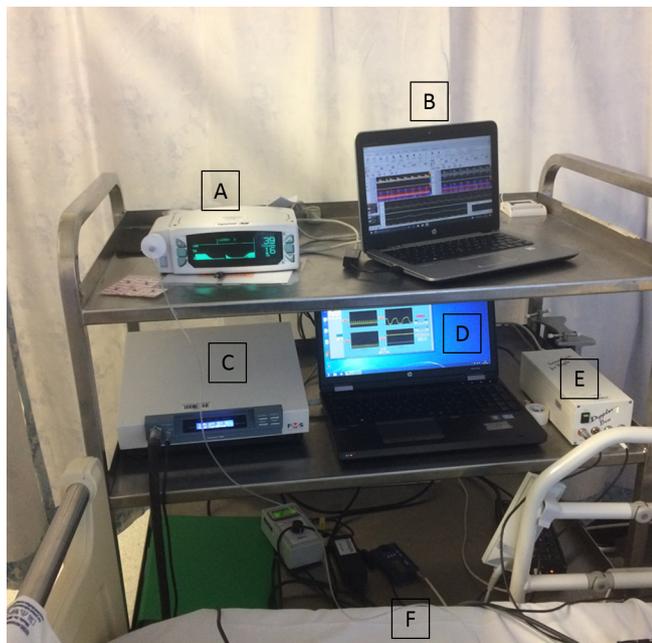


Figure 1 Bedside physiological measurement set-up for BREATHE-ICH study: (A) capnograph; (B) cerebral blood velocity waveforms from Dopplerbox (V.10.5.1 software) dedicated laptop; (C) Finometer; (D) PHYSISAS data acquisition system; (E) DWL Dopplerbox; (F) Korg Metronome.

Plus) to monitor respiration. Simultaneous bilateral insonation of the middle cerebral arteries (MCA) will be performed with the subject lying supine on a couch using transcranial Doppler ultrasound (TCD, DWL Dopplerbox V.10.5.1 software) to measure CBV as the most widely accepted surrogate of CBF in dCA studies.²¹ Using 2 MHz probes, supported by a custom-made frame, the vessel will be located via the temporal bone window, and identified as the MCA by the waveform, its depth, velocity and the direction of flow. All parameters will be simultaneously recorded onto a computer data acquisition system (PHYSISAS) for subsequent off-line analysis. The physiological measurement set-up is demonstrated in figure 1. A CT scan within 48 hours will be analysed for haematoma size, perihæmatoma oedema and intraventricular extension. The assessment of these imaging parameters will be done blinded to any autoregulation data from initial CT or MRI according to the ABC criteria (assess the length, width and depth of haemorrhage in centimetres) associated with the shape of the haemorrhagic lesion (ABC/2 or ABC/3 for regular or irregularly shaped haemorrhage, respectively).²⁵

Data analysis

Following transfer function analysis (TFA), a measure of dCA, ARI, will be calculated. TFA is the most widely used and validated technique of examining the relationship between CBF and BP in the frequency domain. TFA allows quantification of the close transfer of BP fluctuations to CBF, providing an objective measure of dCA. Furthermore, TFA and coherence (linearity between

input and output signals) is calculated using Welch's method. Coherence will be used to determine acceptability of good quality data taking into consideration appropriate number of df.²⁶ Beyond these parameters, phase and gain are calculated giving an explanation as to the timing of input (BP) and output (CBV) signals. Lastly, to derive ARI, a time domain approach is used as described by Tiecks *et al* from a standardised set of curves based on CBV response to sudden step changes in BP following thigh cuff deflation.³ A linear mixed model will be fitted to explore the relationship between EtCO₂ and the dCA parameter ARI in acute ICH; the variability between subjects will be accounted for by incorporating the patient as a random effect.

Statistical analysis

All normally distributed continuous variables will be described as mean (SD) and non-Gaussian with skewness as median (IQR). Comparison of baseline data of patients with acute ICH will be made by the Student's t-test for normally distributed data, or by appropriate non-parametric test. Repeated measures analysis of variance (two-way) will be adopted to test for the effect of hypocapnia on CBV and ARI in patients with acute haemorrhagic stroke.

Study limitations

The study limitations have been carefully considered in the context of current work. First, patients are likely to have mild to moderate stroke severity, as evidenced by neurological impairment (National Institutes of Health Stroke Scale (NIHSS) 5–12) and GCS>8 in similar experimental studies. Furthermore, there is the possibility that in order to comply with the respiratory manoeuvre, patients may have milder stroke severity (NIHSS 1–4). Second, this study will use BP instead of cerebral perfusion pressure to calculate dCA parameters, rather than the more invasive ICP measurement. This is an acceptable approach as we are unlikely to find significantly elevated ICP in this patient population as their neurological status would not permit involvement in the study. Third, we will not be directly assessing the effects of BP-lowering therapy on dCA, so there will remain limited data on the impact of intensive BP lowering on cerebral haemodynamics. Therefore, a mechanistic understanding from a cerebral haemodynamic perspective of different targets for intensive BP lowering is lacking. Fourth, use of nasal cannulae for PaCO₂ measurement has benefits associated with rapid response time to changes, though concerns exist over accuracy compared with face mask measurements.²⁷ Lastly, with reference to TCD studies, changes in CBF can be accurately expressed by CBV, as long as the diameter of the MCA remains constant. This assumption is usually acceptable at normocapnia or mild hypercapnia, but at moderate levels of hypercapnia, as we achieved in our subjects, it is likely that CBV underestimated CBF. There are no studies to date showing MCA diameter change with hypocapnia despite evidence being shown in hypercapnia.²⁸

ETHICS AND DISSEMINATION

Ethics and safety considerations

The East Midlands-Nottingham 1 Research Ethics Committee (REC) reviewed the BREATHE-ICH study protocol. The committee appraised the ethical implications of the intervention that would be carried out during the study and potential impact on patient's rights and well-being. Favourable opinion from the REC means that due care and consideration has been made to preserve patient's rights and the methodology is ethically justified; favourable opinion was provided on 31 August 2017 (17/EM/0283). Further to this, University Hospitals of Leicester NHS Trust provided local research and innovation approval on 25 September 2017.

Informed consent will be obtained from participants in line with recommendations set out in the E6(R1) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidelines.

If the study demonstrates feasibility of improving CA in acute ICH, the experience and knowledge acquired will support future prospective (randomised) controlled trials.

Dissemination

We plan to present all data at national and international conferences. Furthermore, we will also publish the findings in international journals. We expect to publish our initial findings during late 2018. Following the publication of our results participant-level data will be available for collaborations, on request.

Contributors JSM, RBP and TGR participated in the developing and testing of the study set-up, conception of the study, designing the statistical and mathematical analysis, and drafted the manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The East Midlands-Nottingham 1 Research Ethics Committee (17/EM/0283).

Provenance and peer review Not commissioned; externally peer reviewed.

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