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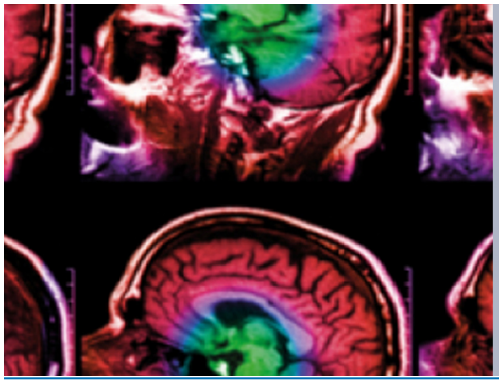

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Cerebrovascular tone and resistance measures differ between healthy control and patients with acute intracerebral haemorrhage: exploratory analyses from the BREATHE-ICH study

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Abstract

Objective. Cerebral autoregulation impairment in acute neurovascular disease is well described. The recent BREATHE-ICH study demonstrated improvements in dynamic cerebral autoregulation, by hypocapnia generated by hyperventilation, in the acute period following intracranial haemorrhage (ICH). This exploratory analysis of the BREATHE-ICH dataset aims to examine the differences in hypocapnic responses between healthy controls and patients with ICH, and determine whether haemodynamic indices differ between baseline and hypocapnic states. *Approach.* Acute ICH patients were recruited within 48 h of onset and healthy volunteers were recruited from a university setting. Transcranial Doppler measurements of the middle cerebral artery were obtained at baseline and then a hyperventilation intervention was used to induce hypocapnia. Patients with ICH were then followed up at 10–14 D post-event for repeated measurements. *Main results.* Data from 43 healthy controls and 12 patients with acute ICH met the criteria for statistical analysis. In both normocapnic and hypocapnic conditions, significantly higher critical closing pressure and resistance area product were observed in patients with ICH. Furthermore, critical closing pressure changes were observed to be sustained at 10–14 D follow up. During both the normocapnic and hypocapnic states, reduced autoregulation index was observed bilaterally in patients with ICH, compared to healthy controls. *Significance.* Whilst this exploratory analysis was limited by a small, non-age matched sample, significant differences between ICH patients and healthy controls were observed in factors associated with cerebrovascular tone and resistance. These differences suggest underlying cerebral autoregulation changes in ICH, which may play a pivotal role in the morbidity and mortality associated with ICH.

Introduction

The impairment of cerebral autoregulation (CA) in acute neurovascular disease states has been well described (Minhas *et al* 2019a). Furthermore, the feasibility and acceptability of improving dynamic CA (dCA) through a targeted intervention has been successfully demonstrated in the BREATHE-ICH study, which investigated patients suffering an acute intracerebral haemorrhage (ICH) (Minhas *et al* 2018a, 2019b). Specifically, the study investigated mild ICH (mean National Institutes of Health Scale score of 4), without intraventricular extension but hypertension at time of presentation (mean systolic blood pressure (BP) greater than 160 mmHg). The BREATHE-ICH study demonstrated that although it is feasible to improve dCA, calculated as the autoregulation index (ARI), through hyperventilation associated hypocapnia during the acute period (<48 h), this was not

sustained in the sub-acute period (10–14 D) (Minhas *et al* 2019b). Therefore, during the highly variable haemodynamic changes that occur in acute ICH, it is unclear whether there are other factors exerting influence either ipsilaterally or contralaterally during the presence of an intracerebral haematoma. A prior meta-analysis demonstrated the existence of lower mean cerebral blood flow velocity (CBFV) and impaired CA in acute ICH, characterising the various autoregulatory indices used to assess CA in ICH (Minhas *et al* 2019a).

The behaviour of key haemodynamic parameters associated with cerebrovascular tone (critical closing pressure, CrCP) and cerebrovascular resistance (resistance-area product, RAP) in acute ICH remains unclear (Minhas *et al* 2019b). These may hold relevance prognostically as haematoma expansion is an important contributing factor to the high mortality and morbidity associated with acute ICH. Unfortunately, the relationship between CA and haematoma expansion has yet to be elucidated, though deterioration in CA between day 3 and 5 has been associated with a worsening 3-month functional stroke outcome (Ma *et al* 2016).

This exploratory analysis of the BREATHE-ICH dataset is designed to: (i) examine the differences in hypocapnic response between healthy controls and patients with acute ICH; (ii) determine for the first time whether haemodynamic indices associated with cerebrovascular tone (CrCP) and cerebrovascular resistance (RAP) differ between baseline and during a well-validated hyperventilation associated hypocapnic intervention.

Methods

Subjects and measurements

The study was conducted in accordance with the Declaration of Helsinki (2013). Ethical approval was obtained from the local university research ethics committee for healthy volunteer recruitment (jm591-c033) and the East Midlands Nottingham 1 Research Ethics Committee for the patient study (17/EM/0283) (Minhas *et al* 2018a). Healthy volunteers were recruited from university departmental staff, students and their relatives. Participants aged above 18 years were included. Exclusion criteria for the healthy volunteer study were physical disease in the upper limb, poor insonation of both temporal bone windows, and any significant history of cardiovascular, neurological, or respiratory disease. Smokers were excluded. Acute ICH patients, able to comply with a respiratory manoeuvre (hyperventilation), were recruited within 48 h of onset and at 10–14 D post-acute stroke. Additionally, the exclusion criteria for the patient study included those with significant previous airways disease (formal diagnosis of moderate or severe airways disease and having treatment for this respiratory condition—via inhalers or specialist input) (Minhas *et al* 2018a, 2019b). The study demonstrated tolerance of the protocol in a cohort of patients with mild supratentorial haemorrhage. All participants provided written, informed consent.

Experimental protocol

The research was undertaken in a research laboratory maintained at a constant ambient temperature of approximately 24 °C and without visual or auditory distraction. For the purposes of the study, participants were requested not to have caffeine and alcohol for a minimum period of four hours prior to measurements being undertaken. Beat-to-beat BP was recorded continuously using the Finometer® device (FMS, Finapres Measurement Systems, Arnhem, Netherlands), which was attached to the left middle finger. The servo-correcting mechanism of the Finometer® was switched on and then off prior to measurements. The hand bearing the finger cuff was at the level of the heart to negate any hydrostatic pressure bias. Heart rate (HR) was recorded using a standard 3-lead electrocardiogram (ECG).

End tidal CO_2 ($EtCO_2$) was continuously measured with small nasal cannulae (Salter Labs) connected to a capnograph (Capnocheck Plus). Transcranial Doppler ultrasound (Viasys Companion III; Viasys Healthcare) with a 2 MHz probe was performed to bilaterally insonate the middle cerebral arteries (MCAs). The probes were placed in position with a head-frame. The MCAs were identified according to two core features: signal depth and velocities.

Measurements were continuously recorded at a rate of 500 samples/s in the PHYSIDAS data acquisition system (Department of Medical Physics, University Hospitals of Leicester NHS Trust). Systolic and diastolic brachial BP readings (OMRON Model 705IT) were performed regularly, at each protocol procedure (normocapnia and hypocapnia) with a minimum of three recordings per individual. These values were then used for calibration of the Finometer output during analysis.

Hyperventilation strategy

Following a 20 min supine rest period, a 5 min supine baseline recording was taken of the subject breathing spontaneously at rest. Hyperventilation strategies were conducted a minimum of once, with repeated assessments conducted where possible, with 5 min intervals between each to allow stabilisation of all parameters and return to normocapnia. The hyperventilation induction strategies involved 60 s of rest, with hyperventilation being maintained for a minimum of 90 s whilst supine. Use of a continuous metronome

(KORG Metronome MA-30), started at a rate in keeping with the subject's baseline resting rate. After 30 s to one minute of baseline recording, the rate was increased gradually over a period of 60 s to reach a hyperventilation rate 40% greater than baseline (around 25 breaths per minute). This was maintained for a further minimum of 60 s and followed by a minimum of 90 s rest.

Data analysis

Data collected corresponded to individual recordings for each participant at baseline and during hypocapnia. First, recordings were inspected visually and calibrated to measured systolic and diastolic OMRON BP. Narrow spikes (<100 ms) were removed using linear interpolation and the CBFV recording was then passed through a median filter. All signals were then low pass filtered with a zero-phase Butterworth filter with cut-off frequency of 20 Hz. Automatic detection of the QRS complex of the ECG to mark the R-R interval was used, but visual inspection was also undertaken with manual correction whenever necessary. This allowed HR, mean arterial blood pressure (ABP) and mean CBFV to be calculated for each cardiac cycle. The peak of the $EtCO_2$ signal was detected and breath-by-breath values were linearly interpolated and resampled in synchrony with the cardiac cycle.

Baseline files were analysed using a moving window autoregressive-moving average (MW-ARMA) model as described by Dineen and colleagues. Initially, an ARMA model is adopted to estimate the CBFV response to a step change in BP and the ARI was estimated by comparison with the 10 template CBFV step responses proposed by Tiecks and colleagues using the first 60 s of data (Tiecks *et al* 1995). The 60 s window was then shifted by 0.6 s and a new estimate of ARI was calculated. This process was repeated until the end of the signal was reached thus generating ARI estimates at each 0.6 s intervals. This produced multiple estimates of ARI, which were then averaged to produce a single baseline ARI value for each file. Having estimates of ARI every 0.6 s is sufficient to represent changes that can take place due to hypocapnia, even at very high respiratory rates caused by hyperventilation, which produce estimates of $EtCO_2$ with time intervals always longer than 2 s. The CrCP and RAP were estimated using the first harmonic method as demonstrated by the two equations provided by Panerai (Panerai 2003).

For the hyperventilation strategy, continuous estimates of ARI were produced for each file using the same MW-ARMA model. These were then digitally marked at the point of $EtCO_2$ increase (signifying the end of hyperventilation) as this proved to be the most recognisable and reproducible point. Marked files were synchronised at 90 s.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, California, USA). The BREATHE-ICH dataset was extracted, cleaned, and only eligible participants were included in further data analysis. Data normality was assessed using the Shapiro-Wilk test. $EtCO_2$ was assumed to follow gaussian distribution. Parametric statistical tests, or their non-parametric equivalents, were then used to compare between baseline and hypocapnic states, and then between healthy controls and patients with ICH. Values of $p < 0.05$ were considered statistically significant.

Results

Key findings

Overall, 43 (19 male, mean age: 33.8 (SD 9.3) years) healthy individuals and 12 [8 male, mean age: 68 (SD 16) years] patients with acute ICH with small volume haematomas (ICH volume mean 5.7 (SD 4.96) ml) met the criteria for statistical analysis. Figure 1 demonstrates a representative data acquisition. Hemispheric comparisons between either left and right sides in healthy participants, or affected and unaffected sides in ICH patients, identified no significant differences. At baseline (normocapnic) measurements, changes in ABP, RAP and CrCP were identified between the healthy participants and the ICH patients. Whereas during hypocapnia, ARI changes were also observed alongside changes in ABP, RAP and CrCP.

Lateralisation

Direct comparisons of the left and right hemispheres of healthy participants found no significant differences between the two sides, for CBFV, RAP, CrCP and ARI in both baseline (normocapnic) and hypocapnic states.

At baseline, no significant differences were identified between the affected and unaffected hemispheres in the patients with ICH at both the initial (<48 h) and follow-up (10–14 D) visits, except for a statistically significantly lower CBFV in the unaffected hemisphere during the follow-up visit (affected 53.9 cm.s [IQR: 38.7, 68.2], unaffected 39.3 cm.s [IQR: 20.4, 59.2], $p = 0.02$). There were no statistically significant differences between the affected and unaffected hemispheres in ICH patients during hypocapnia at both the initial and follow up visits.

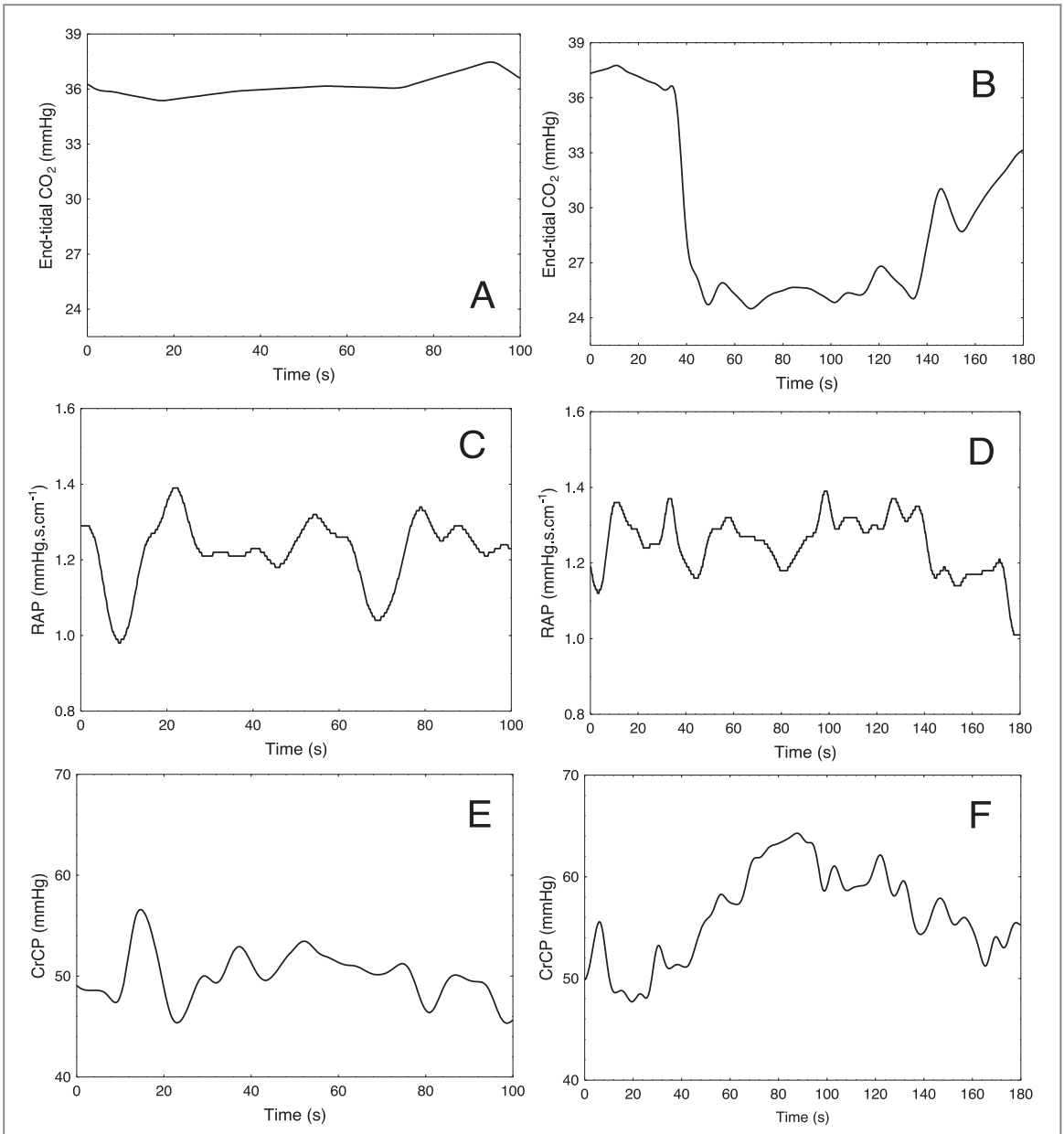

Figure 1. Representative recordings from a 70 year old male patient with a right-sided thalamic intracerebral haemorrhage at rest (A), (C), (E) and during hypocapnia (B), (D), (F). (A), (B) end-tidal CO_2; (C), (D) resistance-area product; and (E), (F) critical closing pressure.

Baseline (normocapnic) haemodynamic characteristics for healthy and ICH

There was a significantly higher mean ABP in ICH patients at <48 h (99.2 mmHg) and 10–14 D (114.3 mmHg) compared to healthy patients (84.3 mmHg) (table 1- baseline). Left and right hemisphere CrCP was greater in ICH patients at <48 h (left 44.9 mmHg, 46.0 mmHg right) and 10–14 D (left 46.1 mmHg, right 44.1 mmHg) compared to healthy controls (left 35.7 mmHg, right 36.9 mmHg; left healthy versus initial $p = 0.018$, right healthy versus initial $p = 0.074$; left healthy versus initial $p = 0.044$, right healthy versus follow-up $p = 0.013$). In addition, left hemisphere RAP was higher in ICH patients at <48 h (1.5 mmHg.s cm^{-1}) compared to healthy individuals (0.95 mmHg.s cm^{-1}) ($p = 0.028$), despite no significant change in ARI. There was no significant difference between CBFV, $EtCO_2$ and ARI (table 1).

Intervention (hypocapnic) haemodynamic characteristics for healthy and ICH patients

The haemodynamic responses to hypocapnic intervention for healthy controls and ICH patients are reported in table 2. A significant reduction in $EtCO_2$ was achieved in the healthy participants using the intervention ($p < 0.001$), and at the initial visit for ICH patients ($p = 0.0210$). However only a non-significant reduction was observed in the ICH patients at their follow-up visit ($p = 0.0651$). There was a significantly higher mean ABP for ICH patients at their initial (92 mmHg) visit compared to healthy patients (84.7 mmHg) ($p = <0.001$).

Table 1. Haemodynamic characteristics for baseline (normocapnic) measurements, with *p*-values from Mann−Whitney U tests (except for $EtCO_2$ which used an unpaired *t*-test).

	Healthy baseline median [IQR]	ICH initial (<48 h) baseline median [IQR]	*P*-value (healthy versus ICH initial)	ICH follow Up (10–14 D) baseline median [IQR]	*P*-value (healthy versus ICH follow up)
Left hemisphere CBFV (cm.s)	54.1 [46.3, 62.7]	44.8 [35.2, 59.9]	0.081	40.2 [32.2, 60.4]	0.154
Right hemisphere CBFV (cm.s)	54.4 [45.7, 62.2]	43.1 [25.2, 61.5]	0.137	42.6 [25.0, 67.3]	0.600
ABP (mmHg)	84.3 [80.3, 94.4]	99.2 [86.1, 111.8]	0.008	114.3 [98.8, 119.5]	<0.001
$EtCO_2$ (mmHg)	36.8 [33.9, 38.1]	36.2 [33.8, 39.9]	0.411	38.2 [34.9, 43.0]	0.0210
Left hemisphere CrCP (mmHg)	35.7 [29.9, 41.2]	44.9 [33.4, 54.3]	0.070	46.1 [34.9, 72.9]	0.028
Right hemisphere CrCP (mmHg)	36.9 [28.6, 43.1]	46.0 [31.6, 64.5]	0.941	44.1 [37.7, 80.3]	0.142
Left hemisphere RAP (mmHg.s cm^{-1})	0.95 [0.71, 1.2]	1.5 [0.83, 1.7]	0.144	1.3 [0.86, 1.9]	0.095
Right hemisphere RAP (mmHg.s cm^{-1})	0.95 [0.77, 1.3]	0.95 [0.7, 1.6]	0.018	1.4 [0.81, 1.7]	0.044
Heart Rate (bpm)	63.4 [58.0, 72.5]	75.1 [58.9, 81.0]	0.074	68.6 [55.2, 72.3]	0.013
Left hemisphere ARI	6.5 [3.7, 7.4]	5.8 [4.2, 7.0]	0.852	4.9 [3.9, 6.9]	0.289
Right hemisphere ARI	6.7 [4.9, 7.4]	4.4 [3,1, 7.1]	0.243	4.4 [3.3, 6.9]	0.125

Values are median [IQR]. CBFV: cerebral blood flow velocity; ABP: arterial blood pressure; $EtCO_2$: end-tidal arterial pressure of carbon dioxide; CrCP: critical closing pressure; RAP: resistance-area product; ARI: autoregulation index. For parameters measured bilaterally, they are listed as either left or right hemisphere measurements.

Table 2. Haemodynamic characteristics for hypocapnic measurements, with *p*-values from Mann−Whitney U tests (except for $EtCO_2$ which used an unpaired *t*-test).

	Healthy hypocapnia median [IQR]	ICH initial (<48 h) hypocapnia median [IQR]	*P*-value (healthy versus initial)	ICH follow up (10–14 D) hypocapnia median [IQR]	*P*-value (Healthy versus Follow Up)
Left hemisphere CBFV (cm.s)	43.1 [38.6, 51.3]	44.4 [33.1, 65.0]	0.680	50.5 [30.9, 58.1]	0.648
Right hemisphere CBFV (cm.s)	42.4 [36.9, 48.7]	38.9 [22.3, 56.2]	0.409	42.1 [24.8, 62.2]	0.982
ABP (mmHg)	84.7 [79.1, 90.9]	92.0 [84.2, 99.6]	0.100	112.8 [97.3, 122.7]	<0.001
$EtCO_2$ (mmHg)	29.9 [26.2, 34.1]	31.6 [27.9, 33.9]	0.850	32.1 [25.2, 35.0]	0.907
Left hemisphere CrCP (mmHg)	40.0 [30.1, 46.8]	51.3 [42.1, 65.4]	0.514	46.7 [30.2, 71.5]	0.260
Right hemisphere CrCP (mmHg)	37.0 [29.5, 45.6]	56.3 [38.6, 80.3]	0.854	50.4 [44.0, 84.8]	0.004
Left hemisphere RAP (mmHg.s cm^{-1})	1.0 [0.83, 1.4]	1.3 [0.75, 1.9]	0.072	1.5 [1.3, 2.2]	0.002
Right hemisphere RAP (mmHg.s cm^{-1})	1.1 [0.87, 1.4]	1.0 [0.82, 1.5]	0.026	1.6 [1.0, 1.9]	0.035
Heart Rate (bpm)	65 [61.8, 75.5]	76.4 [69.2, 80.4]	0.014	70.5 [62.0, 74.3]	0.661
Left hemisphere ARI	8.6 [7.2, 9.0]	6.7 [3.8, 7.8]	0.001	4.2 [3.7, 7.4]	<0.001
Right hemisphere ARI	8.4[7.0, 8.9]	4.1 [3.6, 6.8]	<0.001	4.0 [0.1, 7.1]	<0.001

Values are median [IQR]. CBFV: cerebral blood flow velocity; ABP: arterial blood pressure; $EtCO_2$: end-tidal arterial pressure of carbon dioxide; CrCP: critical closing pressure; RAP: resistance-area product; ARI: autoregulation index. For parameters measured bilaterally, they are listed as either left or right hemisphere measurements.

Differences were also observed in CrCP, RAP, and ARI between healthy participants and ICH patients during hypocapnia. ICH patients at the initial visit had bilaterally higher CrCP (left 51.3 mmHg, right 56.3 mmHg) compared to the healthy participants (left 40.0 mmHg, right 37.0 mmHg), p = 0.026 and 0.014 for the left and right sides respectively. The initial visit also showed a significantly lower ARI bilaterally in ICH patients (left 6.7, right 4.1) compared to the healthy participants (left 8.6, right 8.4) despite similar RAP values; $p = 0.001$ and <0.001 respectively.

At the follow up visit, ICH patients continued to have lower ARI values compared to the healthy participants (left 4.2, right 4.0; $p = <0.001$ bilaterally). RAP values were also noted to be significantly higher compared to healthy volunteers for the left (1.5 mmHg.s cm^{-1} versus 1.0 mmHg.s cm^{-1}; $p = 0.002$) and right (1.6 mmHg.s cm^{-1} versus 1.1 mmHg.s cm^{-1}; $p = 0.035$) hemispheres. A significant difference in CrCP between the healthy and follow up ICH patients was reported for right hemisphere measurements (50.4 mmHg in ICH, 37.0 mmHg in healthy; $p = 0.004$). Lastly, table 3 provides a summary of direct comparisons between normocapnic and hypocapnic results at both the initial and follow-up time periods for patients with ICH.

Discussion

Cerebrovascular tone and resistance in normocapnia

Bilaterally raised tone due to CA

At baseline there is a significantly higher CrCP unilaterally at <48 h and bilaterally at 10–14 D post-ICH compared to healthy patients; suggesting that ICH influences cerebrovascular tone. CrCP reflects changes in cerebrovascular tone and tends to increase with elevations in intracranial pressure (ICP) (Panerai 2003). This supports the significantly raised BP and tone in ICH patients compared to healthy patients (Czosnyka *et al* 1999, Thees *et al* 2002, Sahni and Weinberger 2007, Robertson *et al* 2014, Salinet *et al* 2015, Schlunk and Greenberg 2015). The potential for raised ICP in ICH patients but not in healthy patients could explain the observed rise in CrCP and raised BP in ICH patients.

We propose the that systemic BP drives alterations in CA and cerebrovascular tone (in the absence of changes in ARI). Our results contradict with current evidence suggesting impaired CA for TBI and ICH patients (Reinhard *et al* 2010, Nakagawa *et al* 2011, Ma *et al* 2016, 2017 Lee *et al* 2017, Minhas *et al* 2019b). The reasoning for impaired dCA is currently unknown and there are contradictory studies which have shown preserved CA (Oeinck *et al* 2013).

In this cohort of mild ICH patients, increased CrCP and ABP, coupled with preserved ARI, may be due to the vasoconstrictor cascade aspect of CA that maintains flow perfusion. Panerai (2003) reported that the difference between CrCP and ICP could be explained by the state of arterial vasoconstriction. This suggests ICH induces changes in blood flow distribution by influencing the cerebral vascular network and CA.

We hypothesise that raised tone, and ipsilaterally raised resistance at 10–14 D, may be due to a negative feedback aspect to the myogenic response, via calcium induced hyperpolarisation of ion channels occurring contralaterally, which may reduce the myogenic response and in turn account for the observed lack of change in

Table 3. Haemodynamic characteristics comparing baseline (normocapnic) and hypocapnic measurements in ICH, with *p*-values from Wilcoxon signed-rank tests (except for $EtCO_2$ which used a paired t-test).

	ICH initial (<48 h) baseline median [IQR]	ICH initial (<48 h) hypocapnia median [IQR]	*P*-value (<48 h baseline versus hypocapnia)	ICH follow up (10–14 D) baseline median [IQR]	ICH follow up (10–14 D) hypocapnia median [IQR]	*P*-value (10–14 D baseline versus hypocapnia)
Left hemisphere CBFV (cm.s)	44.8 [35.2, 59.9]	44.4 [33.1, 65.0]	0.365	40.2 [32.2, 60.4]	50.5 [30.9, 58.1]	0.910
Right hemisphere CBFV (cm.s)	43.1 [25.2, 61.5]	38.9 [22.3, 56.2]	0.100	42.6 [25.0, 67.3]	42.1 [24.8, 62.2]	0.313
MAP (mmHg)	99.2 [86.1, 111.8]	92.0 [84.2, 99.6]	0.021	114.3 [98.8, 119.5]	112.8 [97.3, 122.7]	0.910
$EtCO_2$ (mmHg)	36.2 [33.8, 39.9]	31.6 [27.9, 33.9]	0.021	38.2 [34.9, 43.0]	32.1 [25.2, 35.0]	0.065
Left hemisphere CrCP (mmHg)	44.9 [33.4, 54.3]	51.3 [42.1, 65.4]	0.123	46.1 [34.9, 72.9]	46.7 [30.2, 71.5]	0.496
Right hemisphere CrCP (mmHg)	46.0 [31.6, 64.5]	56.3 [38.6, 80.3]	0.700	44.1 [37.7, 80.3]	50.4 [44.0, 84.8]	0.570
Left hemisphere RAP (mmHg.s cm^{-1})	1.5 [0.83, 1.7]	1.3 [0.75, 1.9]	0.608	1.3 [0.86, 1.9]	1.5 [1.3, 2.2]	0.203
Right hemisphere RAP (mmHg.s cm^{-1})	0.95 [0.7, 1.6]	1.0 [0.82, 1.5]	0.831	1.4 [0.81, 1.7]	1.6 [1.0, 1.9]	0.008
Heart Rate (bpm)	75.1 [58.9, 81.0]	76.4 [69.2, 80.4]	0.266	68.6 [55.2, 72.3]	70.5 [62.0, 74.3]	0.672
Left hemisphere ARI	5.8 [4.2, 7.0]	6.7 [3.8, 7.8]	0.831	4.9 [3.9, 6.9]	4.2 [3.7, 7.4]	0.734
Right hemisphere ARI	4.4 [3,1, 7.1]	4.1 [3.6, 6.8]	>0.999	4.4 [3.3, 6.9]	4.0 [0.1, 7.1]	>0.999

Values are median [IQR]. CBFV: cerebral blood flow velocity; MAP: mean arterial blood pressure; $EtCO_2$: end-tidal arterial pressure of carbon dioxide; CrCP: critical closing pressure; RAP: resistance-area product; ARI: autoregulation index. For parameters measured bilaterally, they are listed as either left or right hemisphere measurements.

contralateral resistance (Kiphuth *et al* 2011, Arima *et al* 2012). This may occur to ensure adequate CBF contralateral to the haematoma. This is supported by Ma who suggests vasodilation of downstream vessels must occur to prevent reductions in downstream pressure (Ma *et al* 2017).

Unilateral rise in resistance (RAP)

The unilateral left sided increase in cerebrovascular resistance for ICH patients at 10–14 D follow up, compared to healthy participants conflicts with our current understanding of cerebral haemodynamics (Kinoshita 2016). A rise in BP and compensatory increased cerebrovascular tone, leads to increased cerebral vascular resistance (CVR) to limit CBF. CVR and CPP are tightly regulated to prevent a hypo- or hyperperfusion syndrome (van Mook *et al* 2005). The unilateral rise in RAP may be explained by factors affecting CBF (van Mook *et al* 2005, Lidington *et al* 2018). The cerebrovascular network regulates CBF by responding to three main intrinsic factors: CA, neurovascular coupling (NVC) and CVR (Salinet *et al* 2015). At rest there is evidence of interdependence between these three factors to regulate CBF. Therefore, the bilaterally raised cerebrovascular tone and subsequent unilaterally raised cerebrovascular resistance may occur due to the additive influence of other cerebral haemodynamic regulators besides resistance. This is supported by Panerai (2003) who reported that RAP reflects myogenic activity of the cerebrovascular system coupled with an additional metabolic influence. The unilateral rise in RAP may suggest contralateral CBF is influenced by CA or NVC more so than CVR. When we consider the interdependency of the various aforementioned parameters, ARI is independent from CrCP, RAP or mean values of CBFV or ABP, as demonstrated by multiple studies. CrCP and RAP could show an interdependence, depending on the design of the study. Given its intrinsic relationship (CBFV = [ABP–CrCP]/RAP), of these four different parameters, there are only three degrees of freedom, for each cardiac cycle. However, in each case, depending on which variables are considered, beat-to-beat values of RAP and CrCP can be considered independent, if CBFV and ABP are not physiologically clamped (Panerai 2020).

Alternatively, Ma *et al* (2017) hypothesises the perivascular spaces acting as channels for the cytotoxic metabolic and inflammatory components which develop in response to ICH. Therefore, an ipsilateral nature of RAP may be due to leakage of cytotoxic components closest to the penumbra but not distant enough to induce bilateral changes in RAP (Aronowski and Zhao 2011).

Current ICH management guidelines suggest a balance is required between lowering BP to prevent secondary complications of ICH, against maintaining sufficient BP to prevent ischaemia (Morgenstern *et al* 2010). However, consideration of the cerebral haemodynamic implications of a reduction in BP in patients with ICH is an area yet to be extensively considered. Our findings of a raised ABP coupled with no CA impairment is observed for normocapnic patients, providing evidence that CA alterations (including by BP control) should be considered in the management of ICH patients.

The significance of time

Significant changes in ABP and CrCP were shown to be present at both <48 h and sustained until 10–14 D, in addition to RAP changes during 10–14 D of follow up. The sustained changes in cerebral haemodynamics suggest the metabolic and inflammatory processes which occur following an ICH, are sustained up to but not limited to 10–14 D. The metabolic and inflammatory processes following ICH occur within 72 h of ICH and are associated with secondary complications of ICH. The timely removal of cellular debris by inflammatory cells is important to prevent the inflammatory cell mediated augmentation of secondary damage.

Cerebrovascular tone and resistance following hypocapnia intervention

The effect of hypocapnia on cerebrovascular tone and resistance

Significantly higher CrCP at both <48 h and 10–14 D for ICH patients compared to healthy participants was observed during normocapnia and hypocapnia. The cause for this is uncertain, however suggestions to explain this may include an underlying ICH-induced disturbance to cerebrovascular tone. Alternatively, hypocapnia-induced changes to cerebrovascular tone may play a pivotal role in altering CrCP.

The effects of hypocapnia on cerebrovascular tone are associated with reductions in extracellular $H+$ concentration which in-turn induces vasoconstriction of vascular smooth muscle (Cipolla 2016). CrCP increases with reductions in CO_2. Currently reported cerebrovascular tone changes associated with CO_2 are not distinguished as ipsilateral or contralateral for ICH patients. Hence, further investigation is required to understand the cerebrovascular tone changes observed in this study following hypocapnic intervention for ICH patients.

In addition to influencing CrCP, hypocapnia is known to reduce RAP by vasoconstriction (Grüne *et al* 2015, Minhas *et al* 2018b). RAP has potential to reflect CO_2 influences on CVR. RAP varies inversely with changes in $PaCO_2$. Conflicting evidence exists in which some studies report hypocapnia causing an increase in RAP and improvements to CA by inducing vasoconstriction (Ogoh *et al* 2008, Dineen *et al* 2010, Grüne *et al* 2015,

Minhas *et al* 2018b). Other studies report no change in RAP or CrCP following hypocapnia (Grüne *et al* 2015). These findings are seldom reported in ICH patients. As such, further investigation is required to understand the physiological mechanisms by which ICH influences cerebrovascular tone and resistance.

Bilaterally reduced ARI in hypocapnia

We report bilaterally reduced ARI for ICH patients compared to healthy patients during normocapnia and hypocapnia. Hypocapnia marginally improved CA in ICH patients (table 3). However, when not assessed from the perspective of affected versus unaffected as in prior analyses (Minhas *et al* 2019b), there was not a statistically significant improvement in ARI, solely a trend towards improvement. This aligns with current evidence suggesting hypocapnia improves CA via the induction of vasoconstriction, though larger datasets are needed for validation purposes.

The CO_2 changes associated with CA are shown to be specifically associated with the myogenic and metabolic components of CA. Firstly, we hypothesise the mechanism behind the reduced CA following hypocapnia in ICH patients may be due to the presence of metabolic and myogenic components of CA being influenced by CO_2 for ICH patients. This could be explained by the presence of ipsilateral vasospasm at the haematoma site. The hypothesised presence of vasospasm in intraventricular haemorrhage patients could explain the impaired CA coupled with bilaterally raised tone (Minhas *et al* 2019b). Following ICH, the subsequent development of a haematoma in ICH patients commonly occurs due to continued bleeding from the primary source (Qureshi *et al* 2001, Mayer and Rincon 2005). Secondly, we speculate that ICH results in leakage of haem by-products which could induce vasospasm resulting in impairment of CA at the site of the haematoma. The reduced CA in ICH patients compared to healthy participants supports evidence that impaired CA is a predictor of secondary complications following ICH.

Clinical significance

This study investigating the variations in cerebrovascular parameters between healthy participants and ICH patients during normocapnia and hypocapnia has great clinical relevance. The detected significant increase in CrCP and RAP during both normocapnic and hypocapnic conditions in ICH patients compared to healthy volunteers suggest that cerebrovascular tone and resistance are altered during acute ICH. These exploratory findings are novel, evolve existing non-comparative (disease with healthy controls) findings from the original BREATHE-ICH analysis and generate new hypotheses for future work. This is an important consideration for clinical care of these patients, as raised cerebrovascular tone and resistance may promote haematoma expansion, which can play a pivotal role in increased mortality and morbidity associated with ICH.

Limitations

This study had a small sample size of 55 participants. Further analysis of a larger mixed sex cohort is required to support the findings of this investigation and examine for sub-group differences. The cohort mean age of 33.8 years is also a limiting factor, as age has been shown to influence RAP (Minhas *et al* 2019c). In addition to the age differences of the two cohorts, the ratio of healthy patients to ICH patients was unequal. During the follow-up hypocapnic intervention, a non-significant reduction in $EtCO_2$ was observed in the ICH group. Whilst the cause for this is unclear given the demonstration of a reliable hypocapnic intervention in controls and the initial visit, future studies must strive for a significant difference to ensure any hypocapnia-induced changes are observed.

Conclusion

Current research has centred around the effects of CO_2 on CA in healthy individuals, but a paucity of evidence exists relating to CO_2 changes and tone and resistance measures in patients suffering ICH. This small exploratory analysis demonstrated significant differences in cerebrovascular tone and resistance factors between ICH patients and healthy controls. We believe cerebrovascular tone and resistance factors have a role in CBF regulation in ICH patients, and deserve further consideration in larger clinical studies.

Conflicts

The authors declare that they have no conflict of interest.

Declarations

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NHS, the National Institute for Health Research, or the Department of Health, or the authors' respective organisations.

Data access statement

The data analysed in this study can be obtained by direct request to the Corresponding Author.

Contributions

J I: Data analysis, interpreted the data and prepared the manuscript
A S M: Interpreted the data and prepared the manuscript
M K: Interpreted the data and provided critical review of the manuscript
D S: Radiological review of patient computed tomography scans and critical review of the manuscript
R B P: Designed the study, designed the analysis software, supervised the data analysis, interpreted the data and provided critical review of the manuscript
T G R: Designed the study, interpreted the data and provided critical review of the manuscript
J S M: Designed the study, collected the data, supervised the data analysis, interpreted the data, and prepared the manuscript

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