

# Does induced hypertension reduce cerebral ischaemia within the traumatized human brain?

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## Summary

Recent changes in published guidelines for the management of patients with severe head injury are based on data showing that aggressive maintenance of cerebral perfusion pressure (CPP) can worsen outcome due to extracranial complications of therapy. However, it remains unclear whether CPP augmentation could reduce cerebral ischaemia, a finding which might prompt the search for CPP augmentation protocols that avoid these extracranial complications. We studied 10 healthy volunteers and 20 patients within 6 days of closed head injury. All subjects underwent imaging of cerebral blood flow (CBF), blood volume (CBV), oxygen metabolism (CMRO<sub>2</sub>) and oxygen extraction fraction (OEF) using <sup>15</sup>O PET. In addition, for patients, the EEG power ratio index (PRI), burst suppression ratio and somatosensory evoked potentials (SEP) were obtained and CPP was increased from 68 ± 4 to 90 ± 4 mmHg using an infusion of norepinephrine and measurements were repeated. Following elevation of CPP, CBF and CBV were increased and CMRO<sub>2</sub> and OEF were reduced ( $P < 0.001$  for all comparisons). Regions with a reduction in CMRO<sub>2</sub> were associated with the greatest reduction in OEF ( $r^2 = 0.3$ ;  $P < 0.0001$ ). Although CPP elevation

produced a significant fall in the ischaemic brain volume (IBV) (from 15 ± 16 to 5 ± 4 ml;  $P < 0.01$ ) and improved flow metabolism coupling, the IBV was small and clinically insignificant in the majority of these patients. However, the reduction in IBV was directly related to the baseline IBV ( $r^2 = 0.97$ ;  $P < 0.001$ ) and patients with large baseline IBV showed substantial and clinically significant reductions. CPP augmentation increased the EEG PRI (5.0 ± 1.5 versus 4.3 ± 1.4,  $P < 0.01$ ), implying an overall decrease in neural activity, but these changes did not correlate with the reduction in CMRO<sub>2</sub> and there was no change in SEP cortical amplitude (N20–P27). These data provide support for recent changes in recommended CPP levels for head injury management across populations of patients with significant head injury. However, they do not provide guidance on whether the intervention may be more appropriate at earlier stages after injury, or in patients selected because of high baseline IBV. It also remains unclear whether CPP values below 65 mmHg can be safely used in this population. Clarification of the significance of a reduction in CMRO<sub>2</sub> and neuronal electrical function will require further study.

**Keywords:** ischaemia; hypertension; cerebral perfusion pressure; positron emission tomography; head injury

**Abbreviations:** CBF = cerebral blood flow; CBV = cerebral blood volume; CMRO<sub>2</sub> = cerebral oxygen metabolism; CPP = cerebral perfusion pressure; IBV = ischaemic brain volume; ICP = intracranial pressure; OEF = oxygen extraction fraction; PRI = power ratio index; SEP = somatosensory evoked potentials; ROI = region of interest; SjO<sub>2</sub> = jugular venous oxygen saturation

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## Introduction

Recent changes in the published guidelines for the management of traumatic brain injury (Brain Trauma Foundation,

2003) recommend a lower cerebral perfusion pressure (CPP) level (60 versus 70 mmHg), since aggressive maintenance of

CPP levels above 70 mmHg has been associated with increased cardiovascular and respiratory complications. While there appears a clear overall detrimental effect on outcome, this appears to be related to extracranial effects of therapy. However, these data do not address the specific question of whether increases in CPP above 70 mmHg provide any benefit to the injured brain.

Experimental studies of closed head injury generally report that the infusion of vasopressors results in beneficial changes in regional cerebral blood flow (CBF) (Cherian *et al.*, 1999; Kroppenstedt *et al.*, 2002), but suggest that early neurological outcome is not improved (Talmor *et al.*, 1998). The variable response of the cerebral circulation to the infusion of catecholamines in such experimental studies may be related to the choice of agent, disruption of the blood–brain barrier and failure of autoregulation (Tuor *et al.*, 1986).

The clinical effects of an increase in CPP above 60–70 mmHg using fluid resuscitation and the administration of vasopressors within the human brain remain to be clearly established. Although previous clinical studies have shown clear evidence of regional heterogeneity in terms of CBF and metabolism within the injured human brain (McLaughlin and Marion, 1996; Coles *et al.*, 2002, 2004a), few have examined the effect of induced hypertension. The available clinical data suggest that increases in CPP following head injury and subarachnoid haemorrhage produce improvements in tissue  $pO_2$  within structurally normal brain tissue (Kiening *et al.*, 1997; Sahuquillo *et al.*, 2000) and within focal lesions (Stocchetti *et al.*, 1998). Unfortunately, the focal nature of such measurements does not allow an integrated assessment of short-term benefits of CPP augmentation across the injured brain.

This study aimed to determine whether an increase in CPP has beneficial effects in terms of reducing the incidence of cerebral ischaemia following head injury. This is an important issue, since it is likely to influence our search for improved management. If there are physiological benefits to the brain from CPP augmentation above 70 mmHg, it may be worth finding safer means of achieving such augmentation, in ways that reduce the extracranial complications of therapy. However, if a careful analysis suggests that there are no physiological benefits to the injured brain from CPP elevation above 70 mmHg, even in the short term, the search for safer methods of delivering such therapy would not be justified.

All volunteers included in these studies provided informed consent in accordance with the Declaration of Helsinki, and assent was obtained from the next of kin for all patient studies. All studies were approved by the Local Research Ethics Committee at Addenbrooke's Hospital, Cambridge, UK and by the Administration of Radioactive Substances Advisory Committee of the UK.

## Methods

### Subjects

$^{15}O$  PET studies were undertaken on 10 healthy volunteers (eight male, two female) with a mean (range) age of 30 (18–60)

years and 20 patients within 6 days of head injury with a mean (range) age of 33 (16–68) years (Table 1). Patients had a median (range) post-resuscitation Glasgow Coma Score (Teasdale and Jennett, 1974) of 7 (3–9). In patients we obtained baseline PET data, and following an increase in CPP, PET measurements were repeated. In nine of these patients we were able to obtain EEG and somatosensory evoked potential (SEP) data during the same session (Table 1).

### Clinical protocols

Patients were managed with protocol-driven therapy aimed at maintaining intracranial pressure (ICP) below 20 mmHg and CPP greater than 70 mmHg, as previously described (Menon, 1999) (Please see Appendix I which can be viewed as supplementary data online). In order to achieve target CPP, patients received an infusion of dopamine and/or norepinephrine as determined by the clinical protocol (Please see Appendix II which can be viewed as supplementary data online). Patients who received surgical intervention (CSF drainage or decompressive craniectomy) or second-tier medical therapies [barbiturate coma or moderate hypothermia (33–35°C)] prior to PET imaging are specified in Table 1.

In addition, a fibre-optic right jugular bulb catheter (Baxter, USA) was inserted and its position confirmed radiologically. Samples of arterial and jugular venous blood were drawn for simultaneous measurement of arterial blood gases and jugular venous saturation ( $SjO_2$ ). Using protocol-driven therapy (Menon, 1999),  $SjO_2$  was continuously measured and attempts made to maintain levels above 50%.

### PET

PET studies were undertaken on a General Electric Advance scanner (GE Medical Systems, Milwaukee, WI, USA). Emission data were acquired in 3D mode during a 20-min steady-state infusion of 800 MBq of  $H_2^{15}O$  ( $2 \times 5$ -min frames at the end of the administration), following a 60-s inhalation of 300 MBq of  $C^{15}O$  (single 5-min frame), and in 2D mode during a 20-min steady-state inhalation of 7200 MBq of  $^{15}O_2$  ( $2 \times 5$ -min frames at the end of the administration). Image reconstruction (Kinahan and Rogers, 1989) included corrections for attenuation, scatter, randoms and dead time (Coles *et al.*, 2004b). Parametric maps of CBF, cerebral blood volume (CBV), cerebral oxygen metabolism ( $CMRO_2$ ) and oxygen extraction fraction (OEF) were calculated by inputting simultaneous PET and arterial tracer activity measurements into standard models (Fraczkowiak *et al.*, 1980; Lammertsma *et al.*, 1987). We used a blood–brain partition coefficient for  $H_2^{15}O$  ( $\rho$ ) of 0.95 based on the previous *in vitro* data (Herscovitch and Raichle, 1985) and a small to large haematocrit ratio ( $r$ ) of 0.85 (Phelps *et al.*, 1979).

### Hypertension intervention

All patients were stabilized within the PET imaging suite as defined above, and changes in CPP were produced using an infusion of norepinephrine. All other medications were maintained unchanged during the imaging session. Following a 10-min period of stabilization, baseline images were obtained at a CPP of  $\sim 70$  mmHg. On completion of imaging, the norepinephrine infusion was increased to achieve a CPP of  $\sim 90$  mmHg. Once target CPP was achieved, PET imaging was repeated as described above after a further 10-min period of stabilization. Mean (range) infusion rates for norepinephrine at baseline and during the CPP intervention were 0.07 (0–0.25) and 0.14 (0.05–0.33)  $\mu g/kg/min$  respectively.

Table 1 Patient details

No.	Age (yrs)	Sex	Injury mechanism	Marshall	GCS	Extracranial injuries	Data acquisition	Interval to PET (hr)	Surgery	2 <sup>nd</sup> tier therapies	GOS
1	18	M	Assault	NEML	7		PET, SEP and EEG	38	Craniectomy (REDH)	DC, B & H	MD
2	16	F	RTA	NEML	4		PET, SEP and EEG	40			D
3	53	M	RTA	NEML	8		PET, SEP and EEG	58			MD
4	23	M	Fall	EML	5		PET, SEP and EEG	87		DC	MD
5	41	M	Fall	EML	8	# clavicle, scapula and ribs	PET, SEP and EEG	63	Craniectomy (LEDH), EVD	DC	GR
6	68	F	RTA	EML	8		PET, SEP and EEG	20	Craniectomy (LSDH)	DC	GR
7	36	M	RTA	2	7		PET, SEP and EEG	43			U
8	37	M	Assault	EML	7	Facial #s	PET, SEP and EEG	60	Craniectomy (RICH)	DC	GR
9	21	F	RTA	EML	7	# tibia, fibula and humerus	PET, SEP and EEG	23	Craniectomy (LSDH)	DC	3
10	53	F	RTA	2	7	# humerus and ribs	PET	66			SD
11	26	M	Assault	2	9		PET	86	EVD		MD
12	22	M	RTA	2	4		PET	42			SD
13	23	M	RTA	2	6		PET	45			GR
14	63	M	Fall	EML	5		PET	33	Craniectomy (LICH and temporal lobectomy)	DC	SD
15	45	M	Fall	EML	9		PET	40		DC	MD
16	20	M	Fall	EML	4		PET	39	Craniectomy (RSDH)	DC	D
17	18	M	RTA	3	3	# 1 <sup>st</sup> and 2 <sup>nd</sup> lumbar vertebra	PET	125	Craniectomy (RSDH)	DC & H	SD
18	18	M	RTA	2	3	# patella	PET	58	Craniotomy (R frontal lobectomy)	B	MD
19	40	M	RTA	2	4	# clavicle, 2 <sup>nd</sup> thoracic vertebra and ribs	PET	35			5
20	21	F	RTA	3	7		PET	100			3

RTA = road traffic accident; Marshall category (Marshall *et al.*, 1991); GCS = Glasgow Coma Score (Teasdale and Jennett, 1974); # = fracture; PET = PET with cerebral perfusion pressure intervention; SDH = subdural haematoma; EDH = extradural haematoma; ICH = intracerebral haematoma; EVD = extra ventricular drain; H = moderate hypothermia (core temperature  $\sim$ 34°C); DC = compressive craniectomy; B = barbiturate coma; GOS = Glasgow Outcome Score (Jennett and Bond, 1975); GR = good recovery; MD = moderate disability; SD = severe disability; D = death; U = unknown.

### Image analysis

Images were analysed using custom-designed automated software [Petan (Smielewski *et al.*, 2002)] incorporating elements of Statistical Parametric Mapping [SPM99 (SPM99, 1999), Matlab 5.2 (MathWorks, Natick, MD), Analyze 4.0 (AnalyzeDirect, Lenexa, KA, USA)] and co-registration by multiresolution optimization of mutual information [Department of Radiological Sciences, Guys Hospital, London, UK (Studholme *et al.*, 1996, 1997)]. Individual anatomical images were edited to extract a template that identified brain tissue voxels and excluded extracranial tissue, cerebrospinal fluid and extra-axial haematomas. This brain template was applied to the spatially coregistered, parametric PET images, and used to generate corrected parametric maps.

### Region of interest-based analysis

A region of interest (ROI) map specifying 15 ROIs (based on vascular territories and anatomical structure) was drawn within normalized (Talairach) space (Talairach and Tournoux, 1998) on an MR image (Fig. 1A). This was corrected for individual anatomy and the presence of the major cerebral vessels (based on normalized CT or MR brain templates), and applied to the normalized parametric images. Physiological parameters were expressed as an average for all brain tissue within each ROI. Both CT and PET images obtained in patients provided poor grey–white matter discrimination, making it impossible to segment these anatomical areas in mixed ROIs. Consequently, unweighted mean data values were obtained from mixed grey and white matter ROIs in patients and controls, while recognizing that the effect of tissue heterogeneity on  $^{15}\text{O}$  PET models would result in falsely low CBF and  $\text{CMRO}_2$  values (Herscovitch and Raichle, 1983; Correia *et al.*, 1985; Baron *et al.*, 1989). These data allowed comparison of patients and controls.

### Estimation of ischaemic burden

We used OEF to assess the burden of ischaemia in order to avoid the confounding effects of drug- and injury-induced metabolic suppression on CBF and  $\text{CMRO}_2$ . Although it is difficult to find data that identify critical increases in OEF levels that still allow survival in the setting of ischaemia, we have previously validated a technique for patients with brain injury (Coles *et al.*, 2004a, b). We estimated an individualized critical OEF threshold [ $\text{OEF}_{\text{crit}}$ ; this equated to a cerebral venous oxygen content of 3.5 ml/100 ml] for each subject as follows:

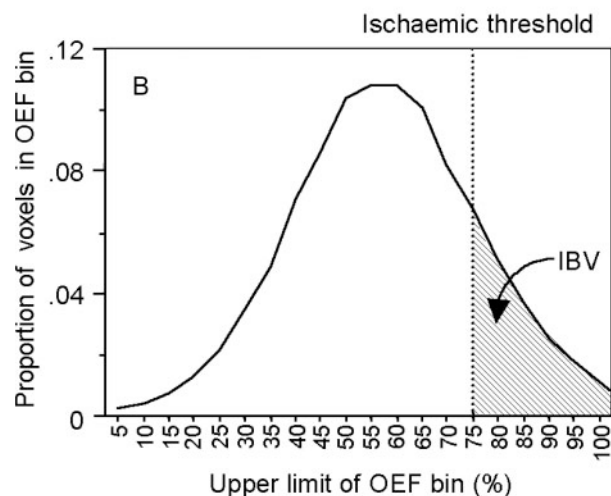
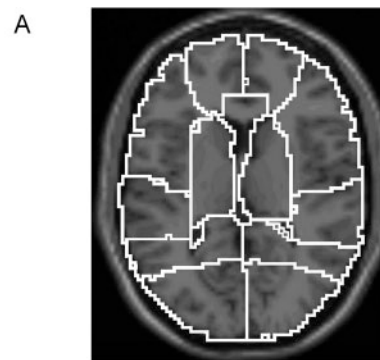
$$\text{OEF}_{\text{crit}} = \frac{(\text{CaO}_2 - 3.5)}{\text{CaO}_2}$$

where

$$\text{CaO}_2 = 1.34\text{HbSaO}_2 + 0.225\text{PaO}_2$$

$\text{CaO}_2$  is cerebral venous arterial oxygen content,  $\text{SaO}_2$  is arterial oxygen content, Hb is the haemoglobin concentration in g/100 ml,  $\text{SaO}_2$  is the fractional arterial oxygen saturation, and  $\text{PaO}_2$  is the partial pressure of oxygen (kPa).

Application of these thresholds to frequency histograms of OEF images allowed us to calculate the volume of voxels with  $\text{CvO}_2$  values below this threshold, and hence allowed estimation of the ischaemic brain volume (IBV) (Fig. 1B). We compared the IBV with data derived from jugular oximetry, using traditional threshold values for  $\text{SjO}_2$  (50%) (Gibbs *et al.*, 1942; Kety and Schmidt, 1948; Robertson and Cormio, 1995; Brain Trauma Foundation, 2000).



**Fig. 1** Methodology. (A) T1-weighted image of reference brain, normalized to Talairach space, indicating the 15 regions of interest (ROIs) defined in the cerebral hemispheres on the basis of anatomical divisions and vascular territories: right and left medial frontal, lateral frontal, temporal, parietal, occipital, deep grey matter, cerebellum and the brainstem. (B) OEF histogram from a single patient, showing the distribution of the number of voxels in each OEF bin. Critical OEF thresholds are derived by calculation of the OEF value above which cerebral venous oxygen content would be less than 3.5 ml/100 ml. The summed volume of voxels with OEF values above this threshold is the IBV.

### Perfusion–utilization matching

OEF values from the 15 ROI template described above should be closely clustered in normal subjects, suggesting efficient matching of CBF to  $\text{CMRO}_2$ , with a resulting narrow spread of OEF values (Lebrun-Grandie *et al.*, 1983). We assessed the matching of oxygen supply to demand in patients using the SD of OEF values across the 15 ROIs and by calculation of the SD of the OEF histograms (SD OEF). These parameters were compared between volunteers and patient groups. Since focal lesions could provide a simple structural cause for abnormal OEF distributions, we also repeated this comparison after excluding ROIs that showed abnormalities on structural CT images.

In addition, we examined the relationships between  $\text{CMRO}_2$  and OEF in order to understand the pathophysiological derangements

induced by trauma. The calculations used to derive CMRO<sub>2</sub> and OEF from <sup>15</sup>O PET make use of common emission data. Consequently, mathematical coupling could confound any exploration of the relationship between these variables. In order to generate data sets that were independent of such effects, we took advantage of the fact that our H<sub>2</sub><sup>15</sup>O and <sup>15</sup>O<sub>2</sub> emission data were collected in two separate frames, and used independent H<sub>2</sub><sup>15</sup>O and <sup>15</sup>O<sub>2</sub> emission and arterial data to calculate mathematically independent CMRO<sub>2</sub> and OEF parametric maps.

### Electrophysiology

Within the PET session, the integrity of neuronal electrical function was assessed using the EEG and measurement of SEP in a subset of patients. The EEG (band pass 0.1–70 Hz) and SEP (band pass 3–3000 Hz) were recorded using two surface electrodes placed bilaterally over the parietal cortex (5 cm posterior to the vertex and 7 cm laterally). To record the local EEG and the SEP primary cortical response (N20–P27), an average reference and an ipsilateral earlobe reference were used, respectively. Electrode impedances were maintained below 5000 Ω. SEP recordings were acquired following median nerve stimulation at the wrist. Ten stimulation intensities were used (10–100 mA in 10 mA increments) to produce a stimulus–response curve separately over the left and right hemispheres. A short interval between stimulus intensities was employed and intensities were repeated if contaminated by noise. Stimuli were presented in a pseudorandom order. A stimulus rate of 4 Hz and duration of 0.2 ms were employed and responses peaking before 200 ms were recorded. At least 450 sweeps were averaged for each SEP recording. Patients with upper limb fractures, which may have influenced SEP measurements, were not recruited.

### EEG analysis

The EEG was assessed using the power ratio index (PRI) method (Nagata *et al.*, 1989), which reflects the ratio of slow to fast wave activity. In patients with an apparent burst suppression pattern (high-amplitude theta/delta activity interrupted by periods of relative quiescence), we calculated a burst suppression ratio by dividing the average duration of quiescence by the average duration of high-amplitude theta/delta activity.

### SEP analysis

SEP waveforms were labelled according to the nomenclature of Mauguere (Mauguere, 1999). The maximal peak-to-trough amplitude of the N20–P27 complex obtained during the sequence of stimulus strengths was recorded.

### Statistical analysis

Statistical analysis was undertaken using Statview© (Version 5, 1998; SAS Institute, Cary, NC, USA). All data are expressed and displayed as mean ± SD, unless otherwise stated. Global, ROI and voxel-based PET data from patient groups and control subjects were compared using two-tailed paired and unpaired *t* tests, and factorial analysis of variance as appropriate. Following statistical advice, individual ROIs were treated independently after Bonferroni correction, since they represented a clinically relevant method of segmenting the brain to look for regional ischaemia, with specific location being irrelevant to this analysis. However, we did not undertake to detect whether ischaemia tended to occur with increased frequency in specific anatomical areas.

It is important to consider how the summary variables that we use to define ischaemic burden (such as IBV) are affected by small changes in individual physiological parameters. Lack of space precludes a full analysis of the subject within the present paper, and we refer interested readers to our previous publications on this topic (Coles *et al.*, 2004a, b).

There was considerable variation in the magnitude and direction of changes in PET-derived metabolic parameters with induced hypertension. These data are therefore displayed as box and whisker plots, and changes were assessed using non-parametric statistics (Wilcoxon signed rank test). Linear regression was used to compare changes in PET physiological parameters, and the relationship between neuronal electrical function and CMRO<sub>2</sub>. Changes in EEG parameters with induced hypertension were assessed using paired *t* tests. All *P* values are quoted after Bonferroni corrections (where appropriate), and corrected *P* values < 0.05 were considered significant.

## Results

### Global physiology

The data for 10 control subjects and 20 patients at baseline and after an increase in CPP are shown in Table 2. When compared with controls, patients showed a significantly lower global CMRO<sub>2</sub> and OEF, and higher CBV. CPP augmentation resulted in a significant increase in CBF and reduction in OEF. In all patients S<sub>j</sub>O<sub>2</sub> remained above 50%.

### Regional physiology

#### ROI analysis

Baseline patient data showed similar CBF, but significantly lower CMRO<sub>2</sub> and OEF and higher CBV when compared with

**Table 2** Global physiology Mean ± SD for CPP, ICP, arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>), S<sub>j</sub>O<sub>2</sub>, global CBF, CBV, CMRO<sub>2</sub> and OEF in 10 healthy controls and 20 patients with head injury

Global data	Control	Baseline in patients	CPP intervention in patients
CPP (mmHg)		68 ± 4	90 ± 4 <sup>##</sup>
ICP (mmHg)		17 ± 5	19 ± 5 <sup>+</sup>
PaCO <sub>2</sub> (kPa)	5.5 ± 0.4	4.4 ± 0.3 <sup>*</sup>	4.5 ± 0.3 <sup>++</sup>
S <sub>j</sub> O <sub>2</sub> (%)		72 ± 7	77 ± 7 <sup>##</sup>
CBF (ml/100 ml/min)	37 ± 5	36 ± 7	39 ± 8 <sup>+</sup>
CBV (ml/100 ml)	3.7 ± 0.8	4.5 ± 0.3 <sup>**</sup>	4.7 ± 0.5
CMRO <sub>2</sub> (μmol/100 ml/min)	123 ± 16	71 ± 13 <sup>*</sup>	68 ± 11
OEF (%)	43 ± 3	36 ± 6 <sup>#</sup>	32 ± 6 <sup>##</sup>

\**P* < 0.001; \*\**P* < 0.01; #*P* < 0.05; unpaired *t* test with Bonferroni correction for comparison between baseline patients and controls. ##*P* < 0.001, +*P* < 0.01, ++*P* < 0.05; paired *t* test with Bonferroni correction for comparison between baseline and CPP intervention.

controls (Fig. 2;  $P < 0.001$  using unpaired  $t$  tests with Bonferroni correction).

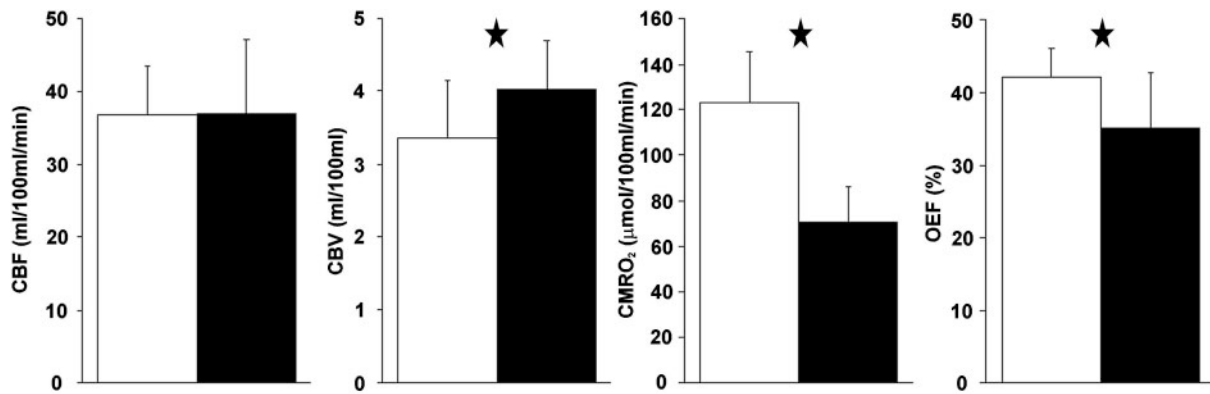
Elevation of CPP to a significant and consistent increase in CBF and reduction in OEF in all subjects (Fig. 3;  $P < 0.001$ ; Wilcoxon signed rank test with Bonferroni correction). Changes in CBV and CMRO<sub>2</sub> were less consistent but showed clear reductions in CMRO<sub>2</sub> and increases in CBV from baseline values (Fig. 3;  $P < 0.001$ ; Wilcoxon signed rank test with Bonferroni correction).

The effects of CPP elevation did not differ between the various anatomical regions of the brain. Although most regions showed a small increase in CBF and fall in CMRO<sub>2</sub>, the regions that showed an increase in CMRO<sub>2</sub> generally came from two patients (patients 9 and 12; Table 1). Examination of the extent of injury and baseline physiology in these subjects did not provide a rational explanation for this finding, and other

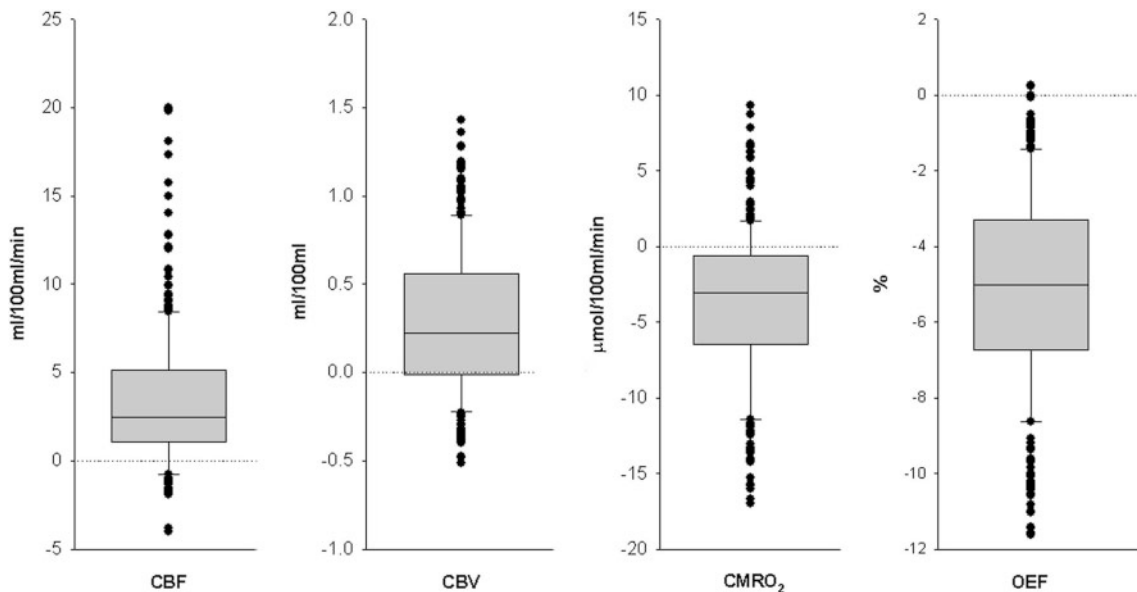
ROIs from the same patients showed changes that were in keeping with those seen in the majority of patients. The effects of CPP elevation upon those regions containing a structural lesion were not significantly different from those that appeared structurally normal. The images from a typical patient at baseline and following induced hypertension are shown in Fig. 4.

### Estimation of ischaemic burden

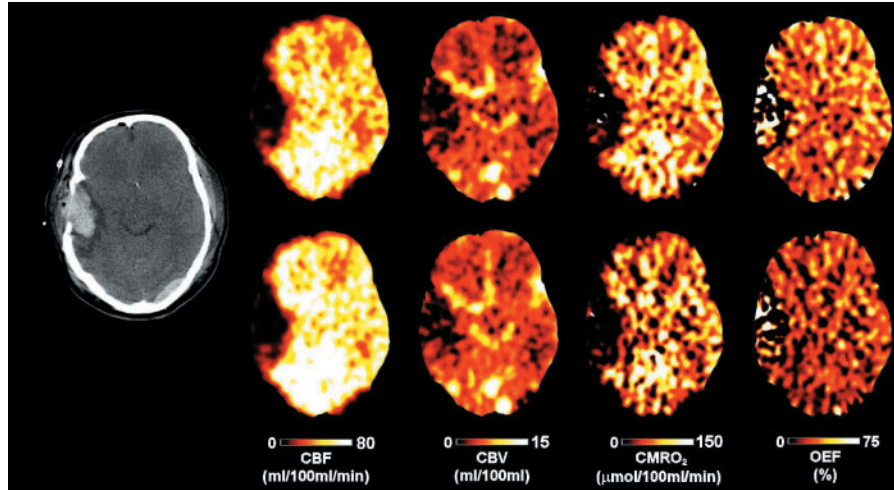
Compared with baseline, the OEF distributions were shifted to the left towards lower OEF values following increased CPP (Fig. 5A). The calculated IBV in controls was significantly lower than in patients at baseline ( $2 \pm 3$  versus  $15 \pm 16$  ml;  $P < 0.05$ , unpaired  $t$  test), and in patients was reduced following CPP elevation (from  $15 \pm 16$  to  $5 \pm 4$  ml;



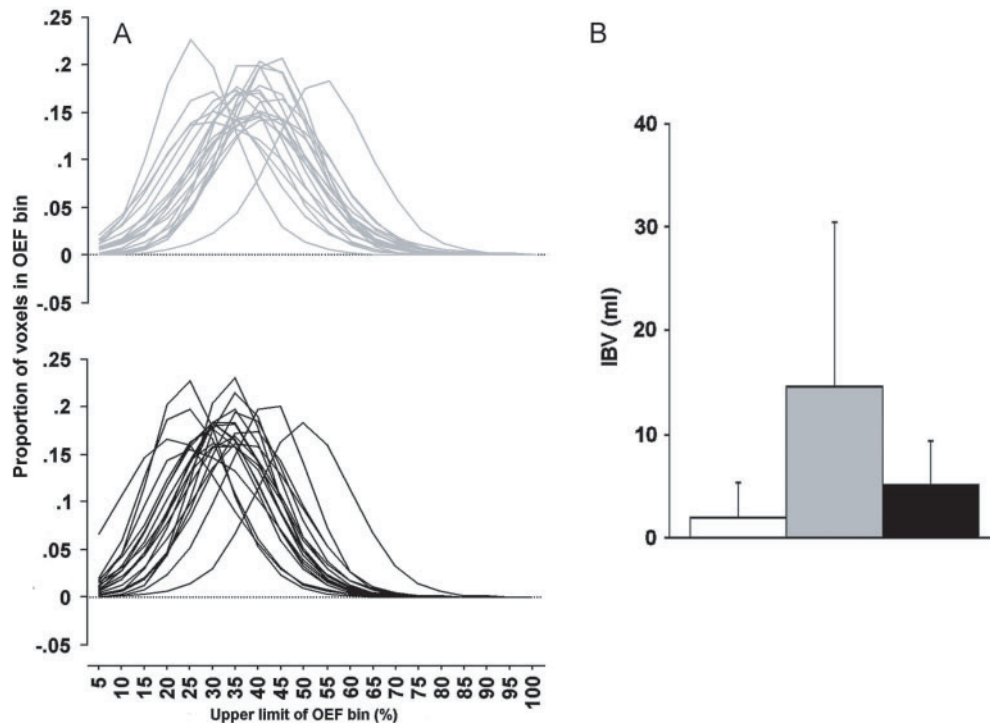
**Fig. 2** Baseline regional physiology. Mean + SD CBF, CBV, CMRO<sub>2</sub> and OEF in ROIs derived from 10 control subjects (white) and from 20 head-injured patients (black). \* $P < 0.001$ ; unpaired  $t$  tests with Bonferroni correction.



**Fig. 3** Effect of hypertension on regional physiology. Box and whisker plots of changes in CBF, CBV, CMRO<sub>2</sub> and OEF produced by an increase in CPP in 15 ROIs in 20 subjects (300 ROIs in total). The central lines in each box denote median values, the lower and upper boundaries the 25th and 75th centiles, the error bars the 10th and 90th centiles, and the closed circles outlying data points. All  $P < 0.001$ ; Wilcoxon signed rank test with Bonferroni correction, comparing baseline and post-hypertension values.



**Fig. 4** PET images following induced hypertension. X-ray CT, PET CBF, CBV, CMRO<sub>2</sub> and OEF images at baseline (top row) and following an increase in CPP (bottom row) obtained 3 days after injury. Note the right temporoparietal haemorrhagic contusion and left occipital extradural haematoma. Baseline ICP was 11 mmHg, CPP 68 mmHg and S<sub>j</sub>O<sub>2</sub> 71%. Following intervention, ICP remained unchanged and CPP and S<sub>j</sub>O<sub>2</sub> increased to 88 mmHg and 76%, respectively. The PET images demonstrate an increase in CBF, reductions in CMRO<sub>2</sub> and OEF and a small increase in CBV with elevation of CPP. The small areas of high signal within the CMRO<sub>2</sub> and OEF images in the area corresponding to the right temporoparietal haematoma are noise-related artefact.

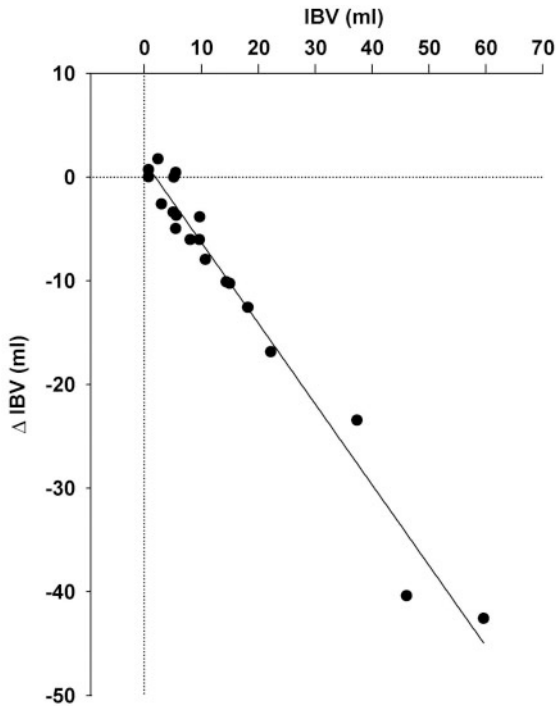


**Fig. 5** Effect of induced hypertension on voxel-based measurements. (A) Individual patient OEF histograms (showing proportion of voxels in each OEF bin) at baseline (grey; mean CPP 68 mmHg) and after an increase in CPP (black; mean CPP 90 mmHg). Note the leftward shift of the curves with an increase in the number of voxels with lower OEF values. (B) Mean + SD ischaemic brain volumes in controls (white), patients at baseline (grey) and after an increase in CPP (black).  $P < 0.01$ ; paired  $t$  test for comparison between baseline and post-intervention values.

$P < 0.01$ , paired  $t$  test) (Fig. 5B). Though the mean change in IBV was small across the group, there were variations between subjects. The maximum volume of potentially ischaemic brain at baseline was 60 ml (5% of brain volume)

and this was reduced to 18 ml (1% of brain volume) following an increase in CPP from 76 to 92 mmHg.

The reduction in IBV with CPP augmentation was significantly related to baseline IBV ( $r^2 = 0.97$ ;  $P < 0.001$ , linear



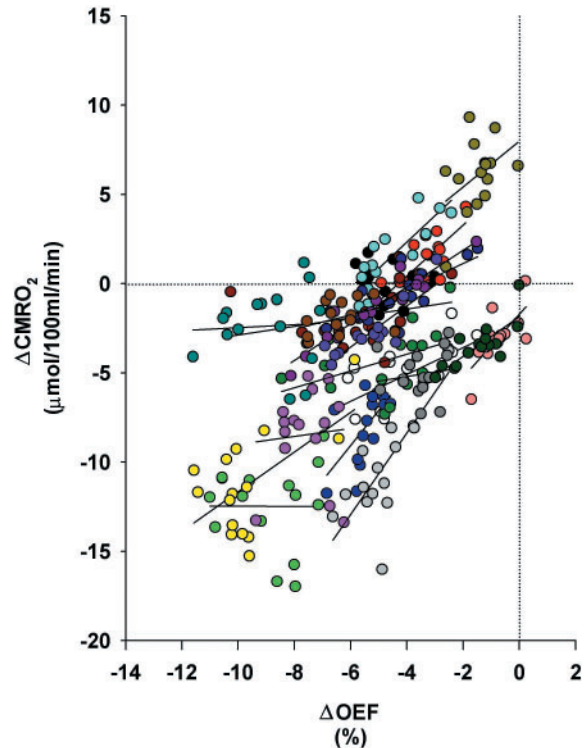
**Fig. 6** Linear regression plot of the relationship between the extent of IBV reduction ( $\Delta$ IBV) and baseline IBV ( $r^2 = 0.97$ ,  $P < 0.001$ ).

regression) (Fig. 6). IBV reduction was not related to time after injury, and the effect of baseline IBV on IBV reduction was maintained in a model that included the change in arterial partial pressure of carbon dioxide and CPP between baseline and intervention ( $P < 0.001$ ; analysis of variance).

### Perfusion utilization matching

OEF values across the 15 regions in individual subjects showed a significantly wider SD in baseline patients than in controls ( $4.9 \pm 1.4$  versus  $3.0 \pm 0.6\%$ ;  $P < 0.001$ ; unpaired  $t$  test), suggesting less uniform and efficient matching of oxygen delivery to demand in the patients. These differences were retained when regions that contained structural lesions were excluded ( $P < 0.001$ ). Following induced hypertension, the SD decreased ( $4.5 \pm 1.1$  versus  $4.9 \pm 1.4\%$ ;  $P < 0.01$ ; paired  $t$  test), implying a small improvement in flow–metabolism coupling. In addition, the SD of the OEF histograms was wider in baseline patients compared with controls ( $14.9 \pm 4.2$  versus  $10.5 \pm 1.5\%$ ;  $P < 0.01$  unpaired  $t$  test), and decreased following induced hypertension ( $13.7 \pm 3.0$  versus  $14.9 \pm 4.2\%$ ;  $P < 0.05$  paired  $t$  test).

Correlation of the change in OEF ( $\Delta$ OEF) and  $\text{CMRO}_2$  ( $\Delta\text{CMRO}_2$ ) showed a significant linear relationship ( $r^2 = 0.3$   $P < 0.0001$ ). The relationship was variable but generally stronger within individual subjects, with a median (range)  $r^2 = 0.37$  (0–0.9) and  $P = 0.02$  (<0.0001–0.99) (Fig. 7). Although this suggests that  $\text{CMRO}_2$  reductions were observed in ROIs



**Fig. 7** Linear regression plot of the relationship between  $\Delta$ OEF and  $\Delta\text{CMRO}_2$  with induced hypertension in 300 ROIs from 20 patients for each individual subject [median (range)  $r^2 = 0.37$  (0–0.9) and  $P = 0.02$  (<0.0001–0.99)].

that showed the greatest decrease in OEF (with no dependence on initial OEF values), it may have been a spurious relationship due to mathematical coupling between the variables used for calculation of  $\text{CMRO}_2$  and OEF (Frackowiak *et al.*, 1980). Following recalculation using independent  $^{15}\text{O}_2$  and  $\text{H}_2^{15}\text{O}$  emission frames to calculate  $\text{CMRO}_2$  and OEF, there was still a significant relationship overall ( $r^2 = 0.06$   $P < 0.0001$ ), and within individual subjects the relationship had median (range)  $r^2 = 0.04$  (–0.09 to 0.34) and  $P = 0.42$  (0.02–0.95).

### Electrophysiology

We were able to obtain bilateral measurements in nine patients. In two patients the EEG measurements were consistent with burst suppression, and therefore we were unable to calculate the PRI. There was no clear relationship between the EEG PRI or maximal SEP amplitude and baseline  $\text{CMRO}_2$  within an ROI that included the primary somatosensory cortex. Following the CPP intervention, there was a significant increase in the PRI ( $4.3 \pm 1.4$  versus  $5.0 \pm 1.5$ ,  $P < 0.01$ ; paired  $t$  test), but the maximal cortical SEP amplitude was similar ( $2.4 \pm 2.0$  versus  $2.4 \pm 1.4$   $\mu\text{V}$ ). In both subjects with a burst suppression EEG pattern, induced hypertension was associated with an increase in the burst suppression ratio (1.38 versus 1.44 and 3.84 versus 4.72). There was no relationship between the  $\Delta$ PRI and  $\Delta\text{CMRO}_2$ .

## Discussion

We combined triple oxygen PET and measurement of neuronal electrical function (EEG and SEP) to examine the effects of an acute increase in CPP using norepinephrine within the first week after clinical head injury. Although an increase in CPP reduced the volume of potentially ischaemic brain and produced some improvement in flow metabolism coupling, the absolute IBV was small in this group of patients. However, the data suggest that in subjects with a large volume of brain at risk of ischaemia and neuronal death, acute elevation of the CPP may be effective in optimizing cerebral perfusion and reducing oxygen extraction. Alongside the reduction in OEF across the brain, we identified a small but significant increase in regional CBF and CBV, and a reduction in CMRO<sub>2</sub>. The relationship between  $\Delta$ OEF and  $\Delta$ CMRO<sub>2</sub> suggests that the reduction in CMRO<sub>2</sub> occurred in those brain regions with the greatest reduction in OEF. The ratio of slow to fast wave EEG activity (PRI) (Nagata *et al.*, 1989) was significantly increased with induced hypertension. While this implied reduced neuronal activity with the CPP intervention, changes in PRI did not correlate with the degree of CMRO<sub>2</sub> reduction. The SEP data were not significantly changed by the increase in CPP. This study provides useful data on the physiological impact of an acute increase in CPP above 70 mmHg using norepinephrine in clinical head injury, and provides a useful context for planning CPP interventions in this setting.

### *Comparison with previous experimental data*

The experimental literature suggests that the effects of catecholamines on cerebral metabolism and CBF are dependent on the choice of agent and dose administered, the state of cerebral autoregulation, and the integrity of the blood–brain barrier (MacKenzie *et al.*, 1976; Tuor *et al.*, 1986). Although norepinephrine would appear to have minimal effects on the cerebral circulation when cerebral autoregulation is intact, following disruption of the blood–brain barrier, it results in an increase in CBF, which cannot be separated from the associated increases in oxygen and glucose metabolism (MacKenzie *et al.*, 1976). These results are consistent with a study that showed that  $\alpha$ -adrenergic agonists resulted in stimulation of metabolism in a primary astrocyte culture (Subbarao and Hertz, 1991), and imply a direct effect on cerebral metabolism. In contrast, the administration of dopamine can result in an increase in CBF and decrease in glucose use within the brain, despite only a moderate increase in mean arterial pressure within the limits of cerebral autoregulation (Tuor *et al.*, 1986).

These experimental studies highlight how responses to vasoactive agents can be highly variable, and provide a framework by which to interpret the results presented in this clinical paper. The clinical protocol for our study required a 20% increase in CPP from a baseline of 70 mmHg. This was easily achieved with fluid management and relatively small doses of norepinephrine (maximum 0.33  $\mu$ g/kg/min). The relatively

small doses required in this study should be compared with the higher doses used in the experimental literature (up to 15  $\mu$ g/kg/min) (Tuor *et al.*, 1986; Kroppenstedt *et al.*, 2002). Some patients received dopamine for control of baseline CPP [mean (range) 2.9 (0–8)  $\mu$ g/kg/min]. The use of dopamine reflects the policy of our institution, where a combination of dopamine and (where necessary) norepinephrine is used to control CPP guided by monitoring of haemodynamic variables. It was deemed clinically and ethically inappropriate to withdraw such medication prior to inclusion in this study. Importantly, the dose of dopamine that patients received was small (maximum 8  $\mu$ g/kg/min) compared with previous experimental studies (up to 300  $\mu$ g/kg/min) (Tuor *et al.*, 1986; Kroppenstedt *et al.*, 2000, 2002), and was not altered throughout the study. Consequently, we investigated the effect of norepinephrine on cerebral physiology, albeit in the presence of a small dose of dopamine in some patients. There was no systematic difference in response to an increase in CPP between those patients who received dopamine and those who did not. It is important to emphasize that it was our intention to conduct a clinical study of the effect of a step increase in CPP on physiology within the injured human brain, and not to test the effects of different catecholamines on cerebral physiology.

### *Hypertension induced metabolic suppression*

It is clear that autoregulation was impaired in our patients since there was a small but consistent increase in CBF and CBV across the brain. However, it is difficult to draw a clear conclusion from the effects on CMRO<sub>2</sub>. Following CPP elevation, there was a small but significant reduction in CMRO<sub>2</sub> across the brain, and only a few brain regions showed evidence of an increase in CMRO<sub>2</sub>. Regions with a reduction in CMRO<sub>2</sub> were associated with the greatest reduction in OEF. This relationship remained significant following exclusion of shared variables within the calculated PET parameters (Frackowiak *et al.*, 1980), despite the lower signal-to-noise characteristics of the independent emission frames used. These results imply that the observed reduction in OEF was due to both an increase in oxygen delivery (consequent to an increased CBF) and a reduction in oxygen demand (evidenced by the reduced CMRO<sub>2</sub>). The former is an expected consequence of our intervention, but the latter effect was unexpected, and not easy to explain.

Experimental studies suggest that the opening of the blood–brain barrier is biphasic following brain trauma (Baskaya *et al.*, 1997), with disruption occurring early (<6 h) and late (~3 days). Although we did not directly measure blood–brain barrier opening, the lack of an increase in CMRO<sub>2</sub> within the majority of brain regions implies that the barrier was intact or the dose of norepinephrine administered was insufficient to have an effect. The patients included were imaged up to 6 days following injury, with two patients imaged within 24 h and 16 within 3 days. Consequently, many had the potential to demonstrate disruption of the blood–brain barrier. We considered the possibility that we may have missed

evidence of regional CMRO<sub>2</sub> increases within injured brain regions. In fact, ROIs that contained evidence of structural injury, based on X-ray CT imaging, were not significantly different from the rest of the brain in terms of their response to hypertension. Although it is possible that we may still have missed evidence of focal CMRO<sub>2</sub> increase within small perilesional regions of oedematous brain, the volume of such tissue is likely to be small. In order to address such issues adequately further studies will be required.

It is interesting to note that MacKenzie and colleagues (MacKenzie *et al.*, 1976) demonstrated a decrease in global CMRO<sub>2</sub> following the infusion of intracarotid norepinephrine in baboons anaesthetized with phencyclidine. Unfortunately the authors did not comment on the significance of this result, which we have replicated in humans. Kuschinsky and colleagues (Kuschinsky *et al.*, 1983) reported decreased glucose metabolism and unchanged blood flow following infusion of norepinephrine to produce a moderate increase in mean arterial pressure in unsedated rats. This result is in contrast to another experimental study by Tuor and colleagues (Tuor *et al.*, 1986) which showed that the relationship between blood flow and glucose use within the brain was unaltered during infusion of norepinephrine to produce moderate hypertension (mean arterial pressure  $\leq$  150 mmHg). It is difficult to draw any summary conclusions from these experimental studies, other than that the effects of systemically administered norepinephrine are dependent on many factors.

The majority of patients in our study were anaesthetized using a combination of propofol and fentanyl, and paralysed with atracurium. It is doubtful that the decrease in CMRO<sub>2</sub> that we describe was related to the effect of increased CPP upon anaesthetic delivery to the brain. In the study by Kuschinsky and colleagues the animals were unsedated (Kuschinsky *et al.*, 1983), and recent experimental data would suggest that an infusion of norepinephrine increases cardiac output and the clearance of propofol (Myburgh *et al.*, 2001). This increased clearance of propofol during norepinephrine infusion does not explain our finding of decreased CMRO<sub>2</sub> in patients with head injury. The only explanation for the reduction in CMRO<sub>2</sub> presented by Kuschinsky and colleagues was of an indirect depression of neuronal electrical function related to the baroreceptor reflex (Bonvallet *et al.*, 1954; Kuschinsky *et al.*, 1983). While this is possible, it clearly requires further investigation.

### Neuronal electrical function

We showed an increase in slow-wave activity in seven patients and an increase in the burst suppression ratio in two others. There was no clear change in the maximum amplitude of the cortical SEP. The experimental literature provides little help in interpreting our data, since the data from previous studies are contradictory. Thus studies have shown both a decrease and an increase in measures of cortical electrical activity following the administration of catecholamines or augmentation of CPP (Dahlgren *et al.*, 1980; Berridge

*et al.*, 1996; Berridge and Abercrombie, 1999; Sebban *et al.*, 1999; Kroppenstedt *et al.*, 2002). Changes in CBF and CMRO<sub>2</sub> were also inconsistent in these studies, but some of these data may have been confounded by changing levels of sedative agents. We did not alter sedative infusions during the CPP intervention, and any changes that we observed with CPP augmentation are likely to have been independent of anaesthetic effects. Although we showed a decrease in CMRO<sub>2</sub> and increase in slow-wave EEG activity, there was no significant correlation between the two within an ROI that included the somatosensory cortex. This suggests that the normal relationship between neuronal electrical function and cerebral metabolism was absent or impaired in these head-injured patients. Although the PET and EEG data we present are consistent with depression of metabolism and neuronal electrical activity, we have no explanation for the cause or significance of these changes.

### Reduction in ischaemic brain volume

Although we identified a significant reduction in the volume of brain at risk of ischaemic injury, it was generally small in this group of patients [mean (range) 15 (1–60) ml]. The small improvement in perfusion utilization matching, demonstrated by the reduction in OEF spread, was small and of limited clinical significance. These results were associated with a significant increase in SjO<sub>2</sub>, and a small but significant increase in ICP. Despite the small changes demonstrated in this study, the significant linear relationship found between the degree of reduction in IBV ( $\Delta$ IBV) and baseline IBV ( $r^2 = 0.97$ ;  $P < 0.001$ ; linear regression) suggests that the greatest benefit of CPP elevation is in those patients found to be at high risk of ischaemia. Any assessment of this relationship is confounded by the fact that baseline IBV and  $\Delta$ IBV are mathematically related; however, we found no such relationship between other physiological variables, such as baseline CBF and  $\Delta$ CBF. Only two patients were imaged within 24 h of injury, and none within 12 h. It is during this early ‘acute’ period that CBF is lowest and patients are at the highest risk of ischaemia (Bouma *et al.*, 1991; Coles *et al.*, 2004a). Further study is required to identify whether an increase in CPP is beneficial in this acute period following head injury or in other subgroups of patients at high risk of ischaemic injury. In addition, we have no data on whether CPP can be safely maintained below 65–70 mmHg, and what constitutes the optimal CPP. It also is important to highlight the limited number of patients that we studied, and recognize that further studies will be required to replicate our results and confirm our findings.

### Conclusions

Recent studies suggest that the risk of extracranial complications dominates outcome effects when conventional techniques of CPP augmentation are used following head injury (Robertson *et al.*, 1999). These effects have been clearly

recognized in recent modifications to the published recommendations for CPP management (Brain Trauma Foundation, 2003). Further, our data suggest that, in most patients, CPP augmentation beyond our baseline levels provides little direct benefit to the injured brain to offset the risks of such treatment.

Importantly, unlike previous experimental studies, we have shown no evidence of direct vasoconstriction or metabolic activation within the human brain following the administration of norepinephrine. In fact, we have demonstrated a reduction in CMRO<sub>2</sub>, which is associated with decreased neuronal electrical function. It remains unclear whether these reductions in CMRO<sub>2</sub> represent a desirable alteration in the balance between oxygen supply and demand, or a reduction in cellular oxidative metabolism that is detrimental to the brain.

However, even allowing for the uncertainties discussed in the previous paragraph, it is possible that CPP augmentation may significantly benefit a small subset of patients in whom PET measurements suggest significant impairments in oxygen supply–demand relationships. It is clearly important to define the pathophysiological phenotype that identifies these patients, so as to employ CPP augmentation in those subjects who potentially have the most to gain. Further studies in subjects within 24 h of head injury or in a specific subset of patients who show high baseline IBV values may allow us to target a patient group in whom the risk/benefit ratio for this intervention is most favourable, and in whom future outcome studies may be most rewarding. Such studies are also required to conclusively prove or disprove our implicit assumption that the reductions in OEF that we demonstrate are beneficial in terms of outcome.

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