Cerebrovascular pressure reactivity is related to global cerebral oxygen metabolism after head injury

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Background: After head injury, impaired cerebrovascular autoregulation has been associated with abnormally high or low cerebral blood flow. The physiological relevance of cerebral blood flow levels is difficult to assess in these patients, whose cerebral metabolic rate for oxygen (CMRO₂) is known to be abnormal. Investigation of these relations requires quantitative measures of cerebral blood flow and CMRO₂, to allow assessment of oxygen supply and demand relations.

Objectives: To investigate the relation between dysautoregulation and global cerebral oxygen metabolism following head injury.

Methods: Using positron emission tomography, global cerebral blood flow, CMRO₂, and oxygen extraction fraction were determined in 22 patients who were investigated in 26 examinations on days 1 to 11 (mean (SD), 3.5 (2.3)) after head injury. Cerebrovascular pressure reactivity was assessed using a pressure reactivity index, calculated as the moving linear correlation coefficient between mean arterial blood pressure and intracranial pressure. Outcome was assessed six months after injury using the Glasgow outcome scale.

Results: Low CMRO₂ was associated with disturbed pressure reactivity (inverse function, $R^2 = 0.21$, $p = 0.018$) and there was a correlation between disturbed pressure reactivity and oxygen extraction fraction (quadratic function, $R^2 = 0.55$, $p = 0.0001$). There was no significant relation between pressure reactivity and cerebral blood flow. An unfavourable outcome was associated with disturbed pressure reactivity. There was no significant relation between outcome and CMRO₂ or oxygen extraction fraction.

Conclusions: There is a close relation between dysautoregulation and abnormal cerebral metabolism but not blood flow. Further studies are needed to determine whether metabolic dysfunction is a result of or a cause of disturbed pressure reactivity, and to establish if there is a relation between cerebral oxygen metabolism and outcome.

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The mechanisms that lead to post-traumatic cerebrovascular dysautoregulation are incompletely understood. In animals, vasoparalysis caused by ischaemia has been shown to abolish autoregulation.¹ Several other mechanisms leading to ischaemia—such as compression of blood vessels by astrocyte swelling,² vasospasm,³ or erythrocyte and leucocyte stasis⁴—have been suggested as causes of dysautoregulation. While other possible mechanisms involve free radicals,⁵ newer work has focused on the role of potassium channel dysfunction,^{6,7} endothelin, and nitric oxide⁸ in autoregulatory failure.

Although the evidence is not unequivocal, several studies have documented an association between disturbed autoregulation and unfavourable outcome after head injury.^{9–12} Despite the fact that dysautoregulation is a result of a multitude of disturbances, it seems reasonable to explain the association of intact autoregulation with good outcome by protection of the injured brain against ischaemia and hyperaemia. There is indirect support for this hypothesis, as Overgaard and Tweed⁹ have shown that in head injured patients low and high cerebral blood flow are associated with impaired autoregulation. While low and high cerebral blood flow have been equated with ischaemia and hyperaemia, such inferences are uncertain in head injured patients, who may show primary changes in metabolism¹³ or be treated with drugs such as propofol and barbiturates or hypothermia. In this setting, measurements of the cerebral metabolic rate for oxygen (CMRO₂) and oxygen extraction fraction are necessary to make the distinction between ischaemia and hyperaemia on the one hand, and metabolically coupled hypoperfusion or

hyperperfusion on the other. Decisions regarding treatment in patients with impaired autoregulation would be facilitated by an understanding of the physiological context in which dysautoregulation is observed. For example, if dysautoregulation were exclusively observed in patients with ischaemia caused by a low cerebral perfusion pressure, blood pressure augmentation could restore normal physiology. On the other hand, if the prominent association of dysautoregulation were with hyperaemia and vasoparalysis, therapeutic strategies would need to be significantly different.

Investigation of these relations requires methods that provide quantitative measures of cerebral blood flow and oxygen metabolism, to allow assessment of the balance of oxygen supply and demand, and enable robust inferences to be made about the presence of ischaemia and hyperaemia. We have used positron emission tomography (PET) to measure cerebral blood flow, CMRO₂, and oxygen extraction fraction, and have compared these variables with an index of cerebrovascular pressure reactivity as a measure of autoregulatory efficiency. The method we used for determination of pressure reactivity calculates a pressure reactivity index (PRx) based on the analysis of spontaneous slow waves of mean arterial blood pressure and intracranial pressure.¹⁴ Our aim in this study was to test the hypothesis that after head injury, disturbed

Abbreviations: CMRO₂, cerebral metabolic rate for oxygen; GCS, Glasgow coma scale; GOS, Glasgow outcome scale; PRx, pressure reactivity index

Figure 1 Schematic illustration of the study protocol. ABP, arterial blood pressure; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate for oxygen; CPP, cerebral perfusion pressure; CT Scan, computed tomography scan for coregistration; ICP, intracranial pressure; OEF, oxygen extraction fraction; PET, positron emission tomography; PRx, pressure reactivity index.

autoregulation is related to disturbed oxygen metabolism—that is, low $CMRO_2$ and oxygen extraction fraction outside the physiological range rather than low or high absolute values of cerebral blood flow.

METHODS

The local research ethics committee approved the study, and informed assent was obtained from the next of kin of all investigated patients.

Patients and clinical management

Between January 1998 and June 2001, we undertook 36 PET examinations in 29 head injured patients who had been admitted to our neurosciences critical care unit and who had continuous monitoring of cerebral pressure reactivity. No patient had more than two PET scans.

All patients were managed with protocol driven treatment aimed at maintaining intracranial pressure below 20 mm Hg and cerebral perfusion pressure above 70 mm Hg. Graded interventions included sedation (propofol, fentanyl) and neuromuscular blockade, rapid surgery for space occupying lesions, drainage of CSF, dopamine or noradrenaline (norepinephrine) for control of cerebral perfusion pressure, mannitol, mild hyperventilation (to a P_aCO_2 of ~4.5 kPa), mild to moderate hypothermia (33–36°C), decompressive craniectomy, and barbiturate coma. A single patient in whom thiopentone (thiopental) had been given during PET was excluded from further analysis. No patient received mannitol in the six hours before PET. Outcome was assessed six months after injury using the Glasgow outcome scale (GOS),¹⁵ with dichotomisation of patients into favourable (good outcome and moderately disabled) and unfavourable (dead, persistent vegetative state, and severely disabled) outcome groups.

Quantification of autoregulatory efficiency using a pressure reactivity index

We used measurements of PRx to assess cerebrovascular pressure reactivity in this group of patients. This method has been described in detail elsewhere.¹⁴ Briefly, for calculation of PRx, the analogue signals of invasive arterial blood pressure monitors and intraparenchymal intracranial pressure transducers were sampled and digitised. Mean arterial blood pressure and intracranial pressure values were calculated over six second intervals using waveform time integration. PRx was calculated every 60 seconds as the moving linear correlation coefficient between the last 40 consecutive six second averages of arterial blood pressure and intracranial pressure. Possible values for PRx therefore range from –1 to +1. Negative or zero values indicate intact pressure reactivity, while increasing positive values indicate increasingly disturbed pressure reactivity. PRx values greater than 0.2 indicate severely disturbed autoregulation and are associated with a poorer outcome.¹⁴ Data analysed in this paper were based on an averaged measurement of PRx over the two hours immediately preceding the PET scan.

Following the two hour period of PRx recording, patients were transported to the PET scanning suite and stabilised before imaging studies were conducted. During acquisition of PRx and PET imaging, haemodynamic stability was ensured by titrating administration of intravenous fluids and if necessary vasoactive agents. To avoid comparing data acquired from different points on a patient's autoregulatory curve, cerebral perfusion pressure during PET scanning was kept as close as possible to the perfusion pressure measured during PRx acquisition. Nine examinations in which the difference in mean perfusion pressure during PET scanning and PRx acquisition exceeded 10 mm Hg were excluded from analysis. The rates of the sedative infusion were left unchanged during acquisition of PRx data and PET imaging. The ventilator settings were adjusted to keep arterial partial pressure of CO_2 ($Paco_2$) constant. The study protocol is illustrated in fig 1.

Positron emission tomography

PET studies were undertaken on a General Electric Advance scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). A 10 minute transmission scan using two rotating $^{68}Ge/^{68}Ga$ rods was done in all patients and used to correct subsequent emission scans for photon attenuation. Emission data were acquired during a steady state infusion of 800 MBq of $H_2^{15}O$, following a 60 second inhalation of 300 MBq of $C^{15}O$, and during a steady state inhalation of 7200 MBq of $^{15}O_2$. Images were reconstructed using the PROMIS 3D filtered back projection algorithm.¹⁶ The emission data were coregistered to spiral computed tomography (CT) images obtained immediately after each PET scan. Parametric maps of cerebral blood flow, cerebral blood volume, $CMRO_2$, and oxygen extraction fraction were calculated by inputting simultaneous PET and arterial tracer activity measurements into standard models, using a capillary to large vessel packed cell volume ratio of 0.85, and a partition coefficient for $H_2^{15}O$ of 0.95.^{17, 18} Images were analysed using custom designed software, incorporating elements of several software packages, including Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>), Matlab 5.2 (MathWorks Inc, Natick, Maryland, USA), Analyze 4.0 (AnalyzeDirect Inc, Lenexa, Kansas, USA), and registration by multiresolution optimisation of mutual information (mpr, Department of Radiological Sciences, Guys Hospital, London, UK^{19, 20}). Individual CT images were edited manually to extract a template that identified brain tissue excluding extracranial tissue, cerebrospinal fluid, and extra-axial haematomas. This brain template was applied to the spatially coregistered PET images, thus restricting analysis to brain tissue. From these data, the global mean values for cerebral blood flow, $CMRO_2$, and oxygen extraction fraction were calculated.

Statistical analysis

Statistical analysis was done using SPSS 10.1 for Windows (SPSS Inc, Chicago, Illinois, USA). Regression methods were used to investigate correlations between PRx and global mean

Table 1 Individual patient data

Patient	Day	GCS	Marshall score	PRx	CPP PRx (mm Hg)	CPP PET (mm Hg)	ICP (mm Hg)	OEF (%)	CMRO ₂ (ml.100ml ⁻¹ .min ⁻¹)	CBF (ml.100ml ⁻¹ .min ⁻¹)	GOS
1a	1	12	NEML	-0.172	81	75	23	59.2	105.9	26.5	4
1b	3			-0.094	77	73	29	35.3	66.3	27.9	
2	3	8	NEML	-0.085	76	76	22	51.2	79.1	28.3	4
3	2	8	DII	-0.090	77	71	15	40.5	70.4	30.6	5
4	7	6	DII	0.409	89	83	25	27.8	49.0	23.4	1
5a	1	5	EML	0.136	80	74	3	45.0	63.5	23.0	4
5b	5			-0.031	77	68	10	46.7	88.1	31.4	
6a	2	9	EML	-0.127	76	75	30	37.9	84.7	36.7	5
6b	5			-0.068	71	75	20	37.1	77.0	35.6	
7	2	4	NEML	0.634	78	79	17	27.3	71.7	41.2	1
8	5	4	NEML	-0.208	79	72	11	42.0	78.6	29.3	3
9	5	12	DII	-0.032	89	98	14	34.9	73.3	28.1	5
10	2	8	EML	-0.122	68	70	14	38.3	100.1	54.4	5
11	3	7	NEML	-0.151	80	86	15	37.7	74.4	32.1	4
12	4	9	NEML	-0.198	87	83	25	45.3	69.7	21.3	5
13	2	7	NEML	-0.142	78	73	11	52.3	91.3	28.2	4
14	2	13	EML	0.089	74	69	14	41.5	83.8	34.9	5
15	11	3	NEML	0.134	85	90	9	32.1	56.8	31.0	3
16	3	8	DII	-0.127	72	75	14	42.1	88.9	28.3	5
17	7	6	NEML	-0.063	95	98	22	40.9	81.7	29.2	3
18	5	6	EML	-0.032	78	82	33	32.3	78.8	42.4	3
19	3	12	NEML	-0.176	84	86	21	46.7	76.6	28.1	3
20	3	8	DII	0.151	87	89	14	31.6	68.9	30.7	3
21a	1	10	NEML	0.007	69	72	20	45.9	87.9	34.0	3
21b	3			0.003	78	73	22	60.2	103.0	26.8	
22	3	12	EML	0.044	67	68	18	29.9	67.1	43.6	5

DII, diffuse injury II; Day, day after injury; CBF, global cerebral blood flow; CMRO₂, global cerebral metabolic rate for oxygen; CPP PET, mean cerebral perfusion pressure during PET scan; CPP PRx, mean cerebral perfusion pressure during PRx acquisition; EML, evacuated mass lesion; GCS, Glasgow coma scale score at admission; GOS, Glasgow outcome scale (1 = dead, 3 = severely disabled, 4 = moderately disabled, 5 = good recovery); ICP, intracranial pressure; NEML, non-evacuated mass lesion; OEF, global oxygen extraction fraction; PRx, pressure reactivity index.

values of cerebral blood flow, CMRO₂, and oxygen extraction fraction. Multiple sampling (four patients were studied twice) was not corrected for, as the interval between these studies was more than 48 hours and with such a delay it is reasonable to assume that the states of autoregulation and cerebral blood flow and oxygen metabolism were independent. For comparisons between outcome and other variables, one way analysis of variance and Spearman rank correlations were used. Numerical data are presented as mean (SD).

RESULTS

Data from 26 examinations in 22 patients were available for analysis. Patients were aged 17 to 64 years (mean 33 (13) years), and their postresuscitation Glasgow coma scale (GCS) score ranged from 3 to 13 (median 8). PET scans were performed one to 11 (mean 3.5 (2.3)) days after injury. There were only two patients with marked disturbance of pressure reactivity (PRx > 0.2). Mean values for global cerebral blood flow, CMRO₂, and oxygen extraction fraction were 31.8 (7.2) ml.100 ml⁻¹.min⁻¹ (range 21.3 to 54.4), 78.3 (13.5) μmol.100 ml⁻¹.min⁻¹ (49.0 to 105.9), and 40.8 (8.7)% (27.3% to 60.2%), respectively. Individual patient data including Marshall scores²¹ are presented in table 1. There were no significant correlations between cerebral perfusion pressure and any of the PET derived variables. Cerebral blood flow was correlated with oxygen extraction fraction ($R = -0.40$, $p = 0.04$) but not with CMRO₂. Oxygen extraction fraction was also correlated with CMRO₂ ($R = 0.71$, $p < 0.0001$). There were no significant correlations between GCS scale and any of the variables measured by PET or between GCS and PRx.

While some patients with positive PRx values showed low global cerebral blood flow, there was substantial interindividual variation (table 1), and there was no significant correlation between cerebral blood flow and PRx (fig 2). The relation between CMRO₂ and PRx was characterised by an inverse function ($R^2 = 0.21$, $p = 0.018$), showing that a very low CMRO₂ in these sedated head injured patients is associated with disturbed pressure reactivity, and that higher CMRO₂ is

associated with better pressure reactivity (fig 3). However, the CMRO₂ relation does not allow us to determine whether the low CMRO₂ values associated with disturbed pressure reactivity were the result of ischaemia or primary metabolic failure. This question was addressed by studying the relation between oxygen extraction fraction and PRx, which can be characterised by a quadratic function ($R^2 = 0.55$, $p = 0.0001$). This model suggests that both low oxygen extraction fraction (representing luxury perfusion, hyperaemia, or necrotic tissue) and high oxygen extraction fraction (representing misery perfusion or ischaemia) are associated with disturbed pressure reactivity (fig 4).

Outcome

Outcome data were available for all 22 patients. Those with unfavourable outcome had worse pressure reactivity (PRx 0.09 (0.28) v -0.09 (0.08); $p = 0.035$) and a higher mean cerebral perfusion pressure (84 (7) v 77 (7) mm Hg; $p = 0.030$). There was a trend for oxygen extraction fraction and CMRO₂ to

Figure 2 Relation between global cerebral blood flow and pressure reactivity (pressure reactivity index). There is no significant relation between global cerebral blood flow and pressure reactivity index in this group of patients, with cerebral blood flow predominantly in the low to normal range.

Figure 3 Relation between global cerebral metabolic rate for oxygen and pressure reactivity (pressure reactivity index). The distribution is characterised by an inverse function. Very low global cerebral metabolic rate for oxygen ($CMRO_2$) in these sedated head injured patients is associated with disturbed pressure reactivity and higher $CMRO_2$ is associated with better pressure reactivity.

Figure 4 Relation between global oxygen extraction fraction and pressure reactivity (pressure reactivity index). A quadratic function represents the best fit to the data. The model suggests that both low oxygen extraction fraction (representing luxury perfusion, hyperaemia, or necrotic tissue) and high oxygen extraction fraction (representing misery perfusion or ischaemia) are associated with disturbed pressure reactivity.

be lower in patients with an unfavourable outcome (38.7% v 42.2% and 75.2 v 80.2 $\mu\text{mol}\cdot 100\text{ ml}^{-1}\cdot\text{min}^{-1}$, respectively) but the differences did not reach statistical significance. The lowest values for oxygen extraction fraction were found in the two patients who died. There were no significant Spearman rank correlations between GOS and PRx ($R = -0.34$; $p = 0.13$), cerebral blood flow ($R = 0.25$; $p = 0.27$), $CMRO_2$ ($R = 0.31$; $p = 0.16$), or oxygen extraction fraction ($R = 0.17$; $p = 0.46$).

DISCUSSION

Our results show a close relation between pressure reactivity, global $CMRO_2$, and oxygen extraction fraction. However, in contrast to earlier studies,⁹ we were unable to demonstrate a relation between measures of autoregulatory efficiency and cerebral blood flow.

Methodological issues

PRx and $CMRO_2$ were clearly related statistically. However, several questions need to be addressed to determine the mechanistic and clinical significance of this relation. It is important to exclude the possibility that the association between $CMRO_2$ and PRx reflected the fact that both low $CMRO_2$ and high PRx are associated with a low GCS— $CMRO_2$ has been shown to correlate with the GCS,²² and earlier work has also shown a correlation between PRx and the GCS.¹⁴ There are several important differences between these earlier studies and the present data which argue against our relation simply being a reflection of GCS. First, we found no relation between GCS and $CMRO_2$ in our data and, in contrast to earlier

studies,²² all our patients were sedated with propofol during measurement of $CMRO_2$. Further, in the data presented here as well as in a recent series of more than 100 patients²³ we found no correlation between GCS and PRx. Interestingly, in the same series of patients there was no correlation between GCS and GOS, possibly reflecting improved prehospital care.

Could our results have been a result of sedation or other confounding variables such as $Paco_2$ or changes in vasoactive drug infusion rates? The wide range of $CMRO_2$ values that we observed despite the fact that all the patients received similar doses of propofol (3–5 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), suggests that sedation with propofol was unlikely to have been the cause of $CMRO_2$ variation between patients. It also seems unlikely that sedation could have been responsible for dysautoregulation, as cerebrovascular autoregulation is well preserved even at much higher doses of propofol.²⁴ Other variables such as $Paco_2$ or temperature were carefully controlled. Infusion rates of dopamine and noradrenaline were adjusted to ensure stability of cerebral perfusion pressure in some patients. There are no data on the potential effects of this on cerebrovascular resistance and therefore autoregulation or, in the case of blood brain-barrier breakdown, on cerebral metabolism through a β adrenergic effect. However, the necessary changes in dose were very small and we chose to adjust the drug rates rather than to tolerate changes in cerebral perfusion pressure that would have made the comparison between PET and autoregulation impossible.

While the association of $CMRO_2$ with PRx is intriguing, these data do not provide a complete explanation of the underlying physiology, as low $CMRO_2$ values may be a result of critical ischaemia or primary metabolic failure. The quadratic function fitted to our oxygen extraction fraction v PRx plot (fig 4) suggests that autoregulation may be impaired in the setting of both ischaemia and hyperaemia, implying that ischaemia and metabolic dysfunction may both provide the substrate for dysautoregulation. Whereas there is no doubt that hyperaemia is associated with loss of autoregulation, there were no patients with relevant global ischaemia represented by a high oxygen extraction fraction in this series, and only eight of our patients had a PRx value above zero. Of those, only two had severely disturbed autoregulation (PRx > 0.2). Therefore, our results—that is, the fitted quadratic function—may be inappropriately influenced by the small number of patients and the location of individual data points.

It is possible to characterise the relation between PRx and oxygen extraction fraction with a linear or inverse function. Based on the fact that it has been shown in animals that ischaemia does lead to loss of autoregulation,¹ it is reasonable to expect a high global oxygen extraction fraction to be associated with a high PRx. However, our data do not allow a definitive conclusion to be drawn. The fact that we were unable to study physiology in severe global ischaemia is testament to the fact that in clinical practice and using a cerebral perfusion pressure orientated approach, ischaemia is easier to control than hyperaemia. This suggests that we may be targeting perfusion pressures too high in some patients, and underscores the need to develop methods that allow optimisation of perfusion pressure in individual patients.

Our cerebral blood flow results disagree with work from Overgaard and Tweed.⁹ It is likely that the relatively small number of patients with predominantly normal cerebral blood flow has prevented us from establishing a correlation, and more data from patients with disturbed autoregulation are needed to characterise the relation between PRx and cerebral blood flow. In view of the large range of ages in this patient group, the analysis was repeated after correcting cerebral blood flow for age, using data from healthy volunteers and the same PET methods described above. However, this procedure did not improve the correlation. Another possible reason for our disagreement with Overgaard *et al* is that they used ¹³³Xe clearance, which predominantly measures blood flow in the

cerebral cortex, whereas our method weights all parts of the brain equally. For technical reasons we could not measure PRx during the PET scan. While cerebral perfusion pressure, sedation, patient temperature, and arterial blood gases were maintained relatively constant, we cannot exclude changes in less obvious confounding variables. While these potential sources of error may have prevented us from observing a relation that was actually present, an alternative explanation is that we were studying a different, more specified population than Overgaard and Tweed.⁹ While their data spanned patients between two hours and 225 days after head injury, our patients were all studied within the first 11 days (mean 3.5 (2.3) days). It may well be that the relation between cerebral blood flow and dysautoregulation that they observed does not hold true in this acute phase. Furthermore, in our patients cerebral perfusion pressure was rigorously controlled, which was not the case in theirs. Alternatively, the absence of a correlation between cerebral blood flow and PRx could also suggest that pressure reactivity relates not to absolute cerebral blood flow levels but to their adequacy in the context of a given level of CMRO₂.

The values for cerebral blood flow and CMRO₂ given in table 1 may seem low, especially when considering that pressure reactivity was intact in the majority of patients. There are several reasons for these low values. First, the injury by itself will reduce CMRO₂ and—where flow–metabolism coupling is intact—cerebral blood flow.²² All patients were sedated with propofol, which will lead to a further reduction in CMRO₂ and blood flow²⁵ without any untoward effects on autoregulation.²⁴ However, it is also important to consider the accuracy of PET derived measures of cerebral blood flow and CMRO₂. The steady state model we have used has been validated in healthy subjects²⁶ and employed by PET centres in a variety of disease states, including acute stroke.²⁷ The steady state model tends to give lower values for cerebral blood flow and CMRO₂ than other techniques.^{28–29} In addition, we report global values and do not segment into grey and white matter. It is well recognised that application of steady state PET models to such heterogeneous regions of interest can result in a significant underestimation of cerebral blood flow and CMRO₂ of up to 20%.¹⁷ In these head injured patients, the PET and CT images did not provide adequate grey/white contrast, and segmentation of structural and functional images was substantially confounded by pathology. Finally, our values may have been affected by the choice of the blood–brain partition coefficient (*p*). The lower the chosen value for *p* the higher the cerebral blood flow and CMRO₂ will be. Despite recent reports that have suggested a value of 0.86,³⁰ the true value is unknown,^{18–31} particularly within diseased brain. We chose to use a *p* of 0.95 based on the previous *in vitro* data.¹⁸ Despite PET being considered the gold standard for imaging cerebral blood flow and cerebral metabolism, the current models do not take into account the changes produced by pathophysiology in head injury and it is not possible to speculate on the error introduced by this limitation. However, none of these factors would result in changes that preclude comparisons within the context of our technique, and do not detract from the validity of our conclusions.

Methodology for measurement of autoregulation

Several techniques have been used to assess autoregulation in head injury, including the measurement of static⁹ and dynamic³² autoregulation in response to step changes in blood pressure. While these methods are well established, they may provide limited information on the response of the cerebral vasculature to smaller changes in cerebral perfusion pressure, which are more common and may be more clinically relevant. Further, they assess the cerebrovascular response at a single time point. We wished to relate PET derived variables to an index of autoregulatory capacity that addressed these issues, and chose a measure of cerebrovascular pressure reactivity for

this purpose. The method we used for determination of pressure reactivity calculates PRx based on the continuous analysis of spontaneous slow waves of arterial blood pressure and intracranial pressure. Vascular pressure reactivity is central to concepts of autoregulation: changes in transmural pressure lead to adjustments in vessel diameter in order to keep cerebral blood flow constant. Pressure reactivity not only represents an important facet of autoregulation, but also has the advantage of being easily measured on-line. There is a strong association between pressure reactivity and autoregulation assessed using transcranial Doppler ultrasonography following head injury.¹⁰

Outcome and clinical implications

Our data confirm earlier work describing a correlation between PRx and outcome.¹⁴ The significant relation between high cerebral perfusion pressure and unfavourable outcome is in agreement with earlier retrospective work showing that managing patients at high perfusion pressures can lead to an unfavourable outcome.²³ We therefore need to address the question of whether overly aggressive augmentation of perfusion pressure may cause a decrease in the oxygen extraction fraction and therefore result in a less favourable outcome. We did not find a significant correlation between oxygen extraction fraction and cerebral perfusion pressure, nor was there an association between low oxygen extraction fraction and an unfavourable outcome. However, our study was neither designed nor powered for that purpose, and larger studies are necessary to address this important clinical question.

It is well recognised that autoregulatory efficiency depends on the level of cerebral perfusion pressure at which it is measured, and conventional intensive care management in head injury is based on increasing the perfusion pressure to a point where restoration of autoregulatory efficiency restores the balance between cerebral blood flow and cerebral metabolism.³³ However, our data raise the intriguing possibility that dysautoregulation may be a consequence as well as a cause of cerebral metabolic failure. If these inferences were confirmed, the critical issue would be to identify patients in whom raising the cerebral perfusion pressure would restore cerebral metabolism to normal, and to differentiate them from those in whom metabolic failure is the primary process. This distinction will depend on the underlying mechanism of the relation. Three scenarios are possible.

The “traditional” model assumes that trauma leads to a disturbance in (microvascular) blood flow and endothelial function, which in turn cause pressure autoregulation to fail. The resultant instability of cerebral blood flow may lead to hyperaemia or ischaemia.

Alternatively, trauma may lead primarily to metabolic dysfunction, possibly reflecting mitochondrial impairment.³⁴ In this instance the decrease in CMRO₂ subsequently leads to dysautoregulation followed by unstable cerebral blood flow and further tissue injury.

Finally, it is possible that pressure reactivity and oxygen metabolism are not functionally related but simply reflect the trauma, with more severe trauma leading to more severe impairment of both variables. Our study was not designed to answer this question, as our data do not permit us to delineate clearly the temporal sequence of events in the pathophysiology of head injury.

Interventional studies that measure autoregulation, cerebral blood flow, and oxygen metabolism before and after step changes in cerebral perfusion pressure will be needed to address these issues. For clinical purposes, determining whether metabolic dysfunction is a cause or a result of disturbed pressure reactivity is important, as manipulating cerebral blood flow or shifting the patient to a more favourable part of the autoregulatory curve can only improve metabolism if the “traditional” model is predominant. Clear evidence that this was the case would strongly support development of an

autoregulation oriented treatment strategy—that is, a strategy based on optimising cerebral perfusion pressure according to an index of autoregulation or pressure reactivity. On the other hand, if metabolic failure were the initial event we might need to focus on pharmacological interventions that improve metabolic (possibly mitochondrial) function. Experimental data provide potential candidates for such interventions.^{35–37}

Conclusions

We have shown that dysautoregulation in head injury is associated with reductions in cerebral oxygen metabolism. In some patients, these associations occur in the context of reduced cerebral blood flow, a finding in keeping with previous investigations in this area. However, we have also demonstrated that in a substantial proportion of patients dysautoregulation is associated with primary metabolic impairment, characterised by CMRO₂ reductions that cannot be attributed to ischaemia. This heterogeneity has implications for our understanding of pathophysiology and our choice of treatment in head injury. Monitoring pressure reactivity in conjunction with metabolic imaging may allow stratification of patients in whom individual disease mechanisms are dominant, allow patient selection for interventional trials using treatments aimed at autoregulation or metabolic dysfunction, and provide information on the response to such treatments. Further studies are needed to investigate the relation between outcome and cerebral oxygen metabolism after head injury.

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