Changes in cerebral oxygen consumption are independent of changes in body oxygen consumption after severe head injury in childhood

D S F Matthews, J N S Matthews, A Aynsley-Green, R E Bullock, J A Eyre

Abstract

This study examines the relation between cerebral O2 consumption (CMRO2) and the O2 consumption of the rest of the body (BVo2) after severe head injury. Seventy-nine serial measurements of whole body O2 consumption, CMRO2, plasma adrenaline, T3, and glucagon concentrations were made in 15 children with severe head injuries receiving neurointensive care. Body O2 consumption was measured with indirect calorimetry and CMRO2 with the Kety-Schmidt technique. There was no evidence of a significant relation between CMRO2 and BVo2. Within each child there were statistically significant positive relations between BVo2 and adrenaline, T3, and glucagon. By contrast, there was only a weak significant positive relation between CMRO2 and T3. In conclusion, CMRO2 and BVo2 seem to be determined independently after severe head injury. Thus therapeutic measures aiming to reduce CMRO2 need to be specific to the brain and it should not be assumed that measures which decrease whole body energy expenditure will necessarily have the same effect on CMRO2.

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Keywords: children; head injury; energy metabolism

Cerebral O2 consumption (CMRO2) accounts for about 20% of total body oxygen consumption in healthy resting adults.1 It is unclear, however, whether the metabolic rate of the brain is closely related to the metabolic rate of the rest of the body either in health or illness. Furthermore, although the mediators influencing whole body metabolic rate have been described,2 it is uncertain whether these mediators affect both cerebral metabolic rate and body metabolic rate in a similar manner. Previous studies within our research group have shown that CMRO2 lies within the normal range for children and decreases significantly in the first 48 hours after severe head injury.3 Robertson et al have shown a similar decrease in whole body O2 consumption (Vo2) over time in adults with severe head injury.4 The aim of this study was to determine if the fall in CMRO2 in our group of children with severe head injury simply reflects changes in whole body metabolic rate as part of the stress response to injury, or whether the fall in CMRO2 indicates independent progressive changes in cerebral function. There are important therapeutic implications because if CMRO2 simply reflects Vo2, general interventions aiming to modify the stress response and reduce metabolic rate will reduce CMRO2 concurrently. If, however, CMRO2 is determined independently from the rest of the body, then specific measures aiming to decrease it are needed. Therapeutic lowering of CMRO2 may benefit those severely head injured children with cerebral hypoperfusion resulting from raised intracranial pressure refractory to conventional treatment.

Patients

The study was part of a larger project examining the hormonal and metabolic response to head injury.3 It was performed on 15 children who had sustained a severe head injury and were receiving neurointensive care. The mean age was 8.8 with a range of 2 to 15 years. Thirteen children had isolated head injuries and two children had other associated injuries. Associated injuries were defined as injuries severe enough to warrant hospital admission in their own right which is roughly equivalent to an Injury Severity Score of ≥ 9.5 In all cases the head injury was the most serious injury sustained. The criterion for admission to the study was a Glasgow coma score ≤ 8.6 In children aged less than 4 years, the adaptation of the Glasgow coma score described by James and Trauner was used.7 The mean Glasgow coma score was 6, range 3 to 8. Table 1 gives further clinical details of the children. Ethical approval for the study was granted by the joint ethics committee of Newcastle Health

Table 1  Clinical details of the 15 children with head injuries

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>GCS</th>
<th>Drugs</th>
<th>Duration of study (h)</th>
<th>No of measurements</th>
<th>Time of first measurement (h)</th>
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<tbody>
<tr>
<td>3-4</td>
<td>F</td>
<td>3*</td>
<td>f1-7-6-7, m 200-270</td>
<td>40</td>
<td>3</td>
<td>9</td>
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<tr>
<td>3-8</td>
<td>M</td>
<td>3</td>
<td>f2-3, m 45-180</td>
<td>79</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>15-6</td>
<td>F</td>
<td>3</td>
<td>f9-9, m 40-75</td>
<td>10</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>10-2</td>
<td>F</td>
<td>4</td>
<td>f2-6-4-3, m 35-100</td>
<td>107</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>14-0</td>
<td>M</td>
<td>7</td>
<td>f2-5-3-8</td>
<td>178</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>6-4</td>
<td>M</td>
<td>6</td>
<td>f1-6-6, m 36-130</td>
<td>79</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>6-4</td>
<td>F</td>
<td>6*</td>
<td>f2-0-4-0, m 50-80</td>
<td>55</td>
<td>6</td>
<td>11</td>
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<tr>
<td>11-5</td>
<td>M</td>
<td>6*</td>
<td>f4-4-5-8, m 85-115</td>
<td>83</td>
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<td>12-0</td>
<td>M</td>
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<td>f6-6-4-3, m 50-75</td>
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<td>9-6</td>
<td>M</td>
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<td>f3-5-3, m 30-100</td>
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<td>9-0</td>
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<td>7</td>
<td>f4-6, m 165-230</td>
<td>5</td>
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<td>14</td>
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<td>11-4</td>
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<td>M</td>
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<td>25</td>
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<tr>
<td>9-9</td>
<td>M</td>
<td>8</td>
<td>f2-5-0, m 50-100</td>
<td>28</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

GCS = Glasgow coma score on admission; f = fentanyl (µg.kg-1.h-1); m = midazolam (µg.kg-1.h-1); * = associated injuries; time of first measurement = time after injury of first measurement.

Authority and University of Newcastle upon Tyne and informed written consent was obtained from the parents.

Management
The clinical care of the children was the responsibility of the neurointensive care team. All children were intubated and received elective intermittent positive pressure ventilation with mild hyperventilation, arterial PCO₂ being maintained between 3.5–4.5 kPa, with a fractional inspired O₂ concentration of 0.3–0.35.

The children were sedated with continuous intravenous infusions of fentanyl (mean 3.4, range 0.6–8.4 μg.kg⁻¹.h⁻¹); 14 children received a simultaneous infusion of midazolam (mean 127, range 33–310 μg.kg⁻¹.h⁻¹). All children received muscle relaxants, either pancuronium or vecuronium. Seven children were given dopamine (mean 0.46, range 0.06–0.80 mg.kg⁻¹.h⁻¹).

Intravenous crystalloid fluids were given at maintenance requirements or with mild fluid restriction (75% of requirements). Nasogastric feeds of a nutritionally complete formula were commenced 24–48 hours after the injury, increasing gradually as tolerated over two to three days.

Rectal temperature was monitored with a rectal probe (Mon-a-Therm Model 6510, Mallinckrodt) accurate to ±0.1°C. The ambient temperature of the intensive care unit ranged from 21–26, mean 24°C. All children had a urinary drainage catheter and peripheral arterial catheter inserted.

Methods
Serial measurements of VO₂ and CMRO₂ were made in each child as soon as possible after admission to the intensive care unit and repeated every six to 24 hours until the child was no longer receiving neurointensive care. These measurements were integrated values determined over a period of 10–20 minutes. Each measurement of VO₂ was followed within 5–20 minutes by measurement of CMRO₂. Simultaneous measurements were not possible because of the requirement for constant volumes of inert gases in inspiratory and expired gases for indirect calorimetry. A blood sample from the indwelling arterial line was taken for determination of plasma concentrations of adrenaline, T3, and glucagon at the end of each measurement of VO₂. All measurements were made during periods of clinical stability, indicated by stable blood pressure, pulse rate, and temperature.

MEASUREMENT OF CEREBRAL OXYGEN CONSUMPTION (CMRO₂)
Global cerebral blood flow was measured by the Kety-Schmidt technique with 10% nitrous oxide as the inert tracer. This method, which is based on the Fick principle, has been described in detail in a previous paper. The reproducibility of the measurement of cerebral blood flow has been shown to be ±3%. At the end of each measurement of cerebral blood flow, arterial and superior jugular venous bulb samples (0.5 ml) were obtained. Blood gas analysis was performed with a Radiometer analyser (Corning 1312) and the oxygen saturation and haemoglobin concentration were measured with a co-oximeter (OSM2 Hemoximeter, Radiometer). Blood oxygen content was calculated according to the equation:

\[
O₂ content = \frac{Hb \times O₂ sat \times 1.39 + (0.023 \times P_O₂)}{}
\]

where Hb = haemoglobin concentration in g.100 ml blood⁻¹; O₂ sat = O₂ saturation expressed as a proportion; P_O₂ = partial pressure of O₂ in kPa

This gives O₂ content in ml.100 ml blood⁻¹. It was then expressed in μmol.ml⁻¹ by multiplying by 0.446.

The CMRO₂ was calculated from the equation:

\[
CMRO₂ = CBF \times (A - V)
\]

where CMRO₂ = cerebral O₂ consumption in μmol.g⁻¹.min⁻¹; CBF = cerebral blood flow in ml.g⁻¹.min⁻¹; A and V = arterial and cerebrovenous contents of O₂ respectively in μmol.ml⁻¹

It should be noted that CMRO₂ does not include energy production via anaerobic metabolism and thus CMRO₂ may underestimate total cerebral metabolic rate. However, using measurements of arterial-cerebrovenous differences in O₂:glucose ratios and lactate concentrations, together with the knowledge that ATP production via glycolysis alone is about 1/18th of the ATP production via glycolysis and the Kreb’s cycle, it can be shown that the ATP production by the brain from anaerobic metabolism accounts for about 4% of total brain energy metabolism, with a maximum of 5%, in this group of children. Thus the effect of anaerobic metabolism on total cerebral energy metabolism is small.

MEASUREMENT OF WHOLE BODY OXYGEN CONSUMPTION (VO₂)
Whole body metabolic rate was measured by indirect calorimetry using a modified Douglas bag technique. This method has been described in detail in a previous paper and will only be outlined briefly. All children were ventilated with a Servo 900 C ventilator using warmed humidified gases. A sample of the inspiratory gases and all the expiratory gases were collected into 51 and 100 l metallised gas bags (Signal Instrument Company, Camberley, Surrey) respectively, over an accurately timed period of 10–20 minutes depending on the minute volume of the child. The bags were then sealed until analysis. One litre of each of the expiratory and inspiratory gases was taken for analysis of O₂ and CO₂ concentrations.

Inspiratory and expiratory O₂ concentrations were measured with a paramagnetic O₂ analyser (Servomex 540A, Servomex, Crowborough, Sussex) modified to analyse discrete 100 ml gas samples and to give a digi-
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Vo2 was calculated from the equation:

\[ \text{Vo2} = \text{VE} \left( \frac{1 - \text{FeO2} - \text{FeCO2}}{1 - \text{FiO2}} \right) \times 20 \times \text{FiO2} - \text{FeO2} \]

where Vo2 is O2 consumption in l.min⁻¹; VE is expired volume in l.min⁻¹ at STPD; FiO2 is proportion of O2 in inspiratory gas; FeO2 is proportion of O2 in mixed expiratory gas; FeCO2 is proportion of CO2 in mixed expiratory gas. Vo2 was then expressed in mmol.min⁻¹ by multiplying by 44.6.

The stability of measurements of Vo2 was assessed in three children, two gas collections being performed at an interval of 20 minutes in each child. The percentage relative errors for Vo2 were 0.5%, 0.4%, and 2%.

MEASUREMENT OF FAT FREE MASS

To explore the relation between CMRO2 and the O2 consumption of the other metabolically active tissues of the body, Vo2 was expressed in terms of kg fat free mass. Fat free mass was calculated from the child's biocentral impedance, measured with a Holtrain body composition analyser (Holtrain Ltd, Crosswell, Dyfed) and the child's height and age. Fat free mass was calculated from the equations of Schaefer et al.

The Vo2 was compared with CMRO2 in mmol.kg brain⁻¹.min⁻¹.

**Statistical Analysis**

Plasma adrenaline concentration had a skewed distribution and underwent logarithmic transformation before analysis.

Analyses based on initial values were made with paired t tests and linear regression techniques. The data set is a mixture of cross-sectional and longitudinal data. To remove the between-child variation and so examine the within-child relations between different variables, the data were analysed with multilevel models fitted using the ML3 program. This methodology is related to multiple regression and produces similar regression coefficients but allows each child to contribute different numbers of observations. Results are available for within-child analyses after centring of explanatory variables.

For graphical presentation, the within-child relations were displayed by calculating the mean for each variable for each child and expressing every observation in terms of the residual from that child's mean. By taking the residuals, the between-child variation was removed and the longitudinal component of the data could be displayed.
Results
A total of 79 serial measurements of VO$_2$, CMRO$_2$ consumption, and plasma hormone concentrations were performed on the 15 children. The median number of measurements performed in each child was five, range two to 11. The median duration of each study was 55 hours, range 5–178 hours. The median time between injury and the first measurement in all 15 children was 11 hours, range 9–42 hours. Table 1 gives further details of the results.

WHOLE BODY OXYGEN CONSUMPTION AFTER SEVERE HEAD INJURY
Figure 1A shows VO$_2$ per kg of fat free mass over the first 120 hours after the head injury. There was a statistically significant fall in VO$_2$ over time from a mean of 0.34 mmol.kg$^{-1}$.min$^{-1}$ at a mean of 12 hours to 0.30 mmol.kg$^{-1}$.min$^{-1}$ at 24 hours after the injury (paired $t$ test $P = 0.005$, 95% CI $-0.063$ to $-0.015$).

There was no evidence of a relation between VO$_2$ and Glasgow coma score on admission ($P = 0.32, r = -0.31$).

There was no evidence for an effect of enteral feeding on VO$_2$. The mean VO$_2$ in the 46 observations made in the unfed state was 0.30 mmol.kg$^{-1}$.min$^{-1}$, whereas the mean VO$_2$ in the 33 observations made in the fed state was 0.31 mmol.kg$^{-1}$.min$^{-1}$ (unpaired $t$ test $P = 0.40$, 95% CI for difference $-0.04$ to $0.02$).

CEREBRAL OXYGEN CONSUMPTION AFTER SEVERE HEAD INJURY
Figure 1B shows CMRO$_2$ over the first 120 hours after the head injury. There was a tendency for CMRO$_2$ to decrease over time from a mean of 1.15 mmol.kg$^{-1}$.min$^{-1}$ at a mean of 12 hours to 1.04 mmol.kg$^{-1}$.min$^{-1}$ at 48 hours but this decrease did not achieve statistical significance (paired $t$ test $P = 0.31$, 95% CI $-0.28$ to $0.097$). The CMRO$_2$ was within the reference range for normal resting children for 78 measurements and depressed for one measurement.$^{21}$

Over the first 120 hours after the head injury, mean cerebral blood flow was 0.47 l.kg$^{-1}$.min$^{-1}$, with a range of 0.18–1.8 l.kg$^{-1}$.min$^{-1}$. There was a statistically significant increase in cerebral blood flow over time from a mean of 0.36 l.kg$^{-1}$.min$^{-1}$ at 12 hours to 0.54 l.kg$^{-1}$.min$^{-1}$ at 48 hours after the injury (paired $t$ test $P = 0.006$, 95% CI 0.05 to 0.25). Cerebral blood flow was within the reference range for normal children for 62 measurements, depressed for 16, and raised in one measurement.$^{21}$ Thus the changes that occurred in CMRO$_2$ over time were not associated with parallel changes in cerebral blood flow.
flow and there was evidence of absolute hyperaemia in only one measurement.

Initial values of CMRO₂ showed a significant positive correlation with Glasgow coma score (P = 0.006, r = 0.71) indicating that the most severely injured children had the lowest cerebral metabolic rates.

There was no evidence of a relation between cerebral blood flow on admission and Glasgow coma score (P = 0.44, r = 0.216).

**BODY OXYGEN CONSUMPTION INDEPENDENT OF BRAIN AFTER SEVERE HEAD INJURY**

Figure 1C shows BVo₂ per kg fat free mass over the first 120 hours after the head injury. There was a significant fall in BVo₂ from mean 0.30 mmol·kg⁻¹·min⁻¹ at a mean of 12 hours to mean 0.26 mmol·kg⁻¹·min⁻¹ at 24 hours (paired t test P = 0.02, 95% CI −0.066 to −0.005).

There was no evidence of a relation between BVo₂ on admission and Glasgow coma score (P = 0.13, r = −0.46).

**CEREBRAL OXYGEN CONSUMPTION AS A PERCENTAGE OF TOTAL BODY OXYGEN CONSUMPTION AFTER SEVERE HEAD INJURY**

Figure 1D shows cerebral O₂ consumption as a percentage of Vo₂(CMRO₂/Vo₂) over the first 120 hours after the head injury. The total CMRO₂ accounted for a mean of 17% Vo₂ with a wide range of 5–34%.

There was no evidence of a significant change of the percentage of Vo₂ accounted for by CMRO₂ from 12 hours, mean 17.6%, until 24 hours, mean 18.6% (paired t test P = 0.95, 95% CI −3.93 to 4.18) and 48 hours, mean 18.2%, after the injury (paired t test P = 0.76, 95% CI −3.10 to 4.12).

There was a statistically significant relation between the percentage of Vo₂ accounted for by CMRO₂ on admission and Glasgow coma score (P = 0.007, r = 0.73). As the percentage of Vo₂ accounted for by CMRO₂ may change with age, the effect of age on the relation was analysed by multiple regression. The significant positive relation between CMRO₂/Vo₂ and Glasgow coma score remained (P = 0.005).

**RELATION BETWEEN CEREBRAL OXYGEN CONSUMPTION AND BODY OXYGEN CONSUMPTION**

There was no evidence of a significant relation between CMRO₂ and BVo₂. Analysis of the raw data showed an apparent negative relation between CMRO₂ and BVo₂ (regression coefficient = −0.16, 95% CI −0.24 to −0.08)
but there are statistical problems interpreting this regression as $\text{BV}_2$ must be calculated by subtracting the total CMRO$_2$ from VO$_2$. The observed metabolic rates differ from the true values by errors of measurement, and the presence of the error in the CMRO$_2$ on both sides of the regression will induce a negative bias in the estimate of the regression coefficient. A heuristic approach to correcting this bias is outlined in the appendix. The adjusted regression coefficient is 0·01 with interval estimates of 0·10 to 0·11, indicating no evidence of a relation between CMRO$_2$ and $\text{BV}_2$.

The CMRO$_2$ and $\text{BV}_2$ are used to indicate cerebral metabolic rate and body metabolic rate independent of brain. This is generally acceptable as the most important measurement of energy expenditure is O$_2$ consumption. After injury, however, respiratory quotient (RQ) values, which reflect the type of fuel oxidised, may be quite variable and thus have a moderate effect on the relation between metabolic rate and O$_2$ consumption. The RQ of the brain may be taken as 1. Glucose, the predominant fuel of the brain has an RQ of 1, and the ketone bodies $\beta$-hydroxybutyrate and acetoacetate give a combined RQ of about 1 if they are utilised in roughly equal quantities. The RQ of the whole body varied from 0·7 to 1·0 in this study with an interquartile range of 0·77 to 0·82. If the RQ of the brain is taken as 1, the RQ of the rest of the body can be calculated from the formula:

$$\text{RQ}_{\text{total}} = \lambda \times \text{RQ}_{\text{brain}} + (1 - \lambda) \times \text{RQ}_{\text{body}}$$

where $\lambda = \text{CMRO}_2(\text{total})/\text{VO}_2$

The total energy expenditure of the brain and the rest of the body could then be calculated from the Weir formula. From these results, which allow for the effects of oxidation of different fuels within the body, it could be shown that there was no evidence for a positive relation between cerebral metabolic rate and the metabolic rate of the rest of the body.

**Table 2 Details of analysis by multilevel modelling (within-child relation between $\text{BV}_2$ and CMRO$_2$, and possible mediators)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\text{BV}_2$ Regression coefficient (Standard error)</th>
<th>$\text{CMRO}_2$ Regression coefficient (Standard error)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Log$_{10}$ adrenaline</td>
<td>0·032 (0·0085)</td>
<td>0·0092 (0·071)</td>
<td>0·89</td>
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<tr>
<td>T3</td>
<td>0·023 (0·0096)</td>
<td>0·015 (0·068)</td>
<td>0·023</td>
</tr>
<tr>
<td>Glucagon</td>
<td>0·0013 (0·0005)</td>
<td>0·0047 (0·0035)</td>
<td>0·18</td>
</tr>
</tbody>
</table>

**Figure 3** Within-child relation between CMRO$_2$, and possible mediators. Each graph shows the residuals from the mean for CMRO$_2$ and each possible mediator. (A) Log$_{10}$ adrenaline, (B) T3, and (C) glucagon.
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Discussion

In our study there was no evidence of a positive relationship between CMRO₂ and BVOC after severe head injury in children. To the best of our knowledge, this relation has not been examined before in either healthy or injured children.

The absence of a positive relation between CMRO₂ and BVOC was supported by the finding that the percentage of Vo₂ accounted for by CMRO₂ varied considerably both between and within children, regardless of the age of the child with the most severely injured children having the lowest percentage of Vo₂ accounted for by the brain.

From experimental work, there is accumulating evidence that the prefrontal cortex and sympathetic nervous system may be important in influencing energy balance in the whole resting animal. The central nervous effect on resting metabolic rate is largely mediated by circulating thyroid hormones and adrenaline, which affect all somatic tissues. The environment of the brain, however, is likely to be different from the rest of the body, largely because of the presence of the blood-brain barrier. Thus it is possible that the metabolic rate of the brain and the rest of the body may be determined independently in health. After severe head injury, local factors induced by trauma and stress may also have important influences on CMRO₂ without affecting BVOC, thus reducing the likelihood of finding a close positive relation between CMRO₂ and BVOC.

In our study, the hormonal mediators shown to have a stimulatory effect on BVOC were adrenaline, T₃, and glucagon. The positive effects of the hormones on BVOC may be predicted from knowledge of their action at a cellular level, and from results of studies of the systemic administration of these hormones.

By contrast with BVOC, the only mediator shown to have a positive effect on CMRO₂ was T₃. This suggests that CMRO₂ is not determined by the whole body stress response after head injury.

A question of fundamental importance is the integrity of the blood-brain barrier after head injury. In normal circumstances the blood-brain barrier is impermeable to catecholamines and glucagon but there is a specific carrier enabling T₃ to cross into brain tissue. If the blood-brain barrier remained intact after head injury, the relations between CMRO₂ and plasma hormone concentrations could be readily explained. Many stressful events in experimental animals, including hypoxia, immobilisation, and sepsis, however, have been shown to result in a raised CMRO₂, where it is proposed that the integrity of the blood-brain barrier is disrupted allowing catecholamines to cross into the brain and stimulate CMRO₂. The blood-brain barrier has been shown to be disrupted in experimental head injury. There is evidence, however, that the disruption tends to be focal and, although the duration of the perturbation may vary, it is probably short lived. These conclusions would be supported by the findings in the present study of a lack of relation between CMRO₂ and high systemic concentrations of catecholamines.

Impaired utilisation of O₂ has been found globally in septic shock and in the brain after head injury (unpublished data). The CMRO₂ was positively related with Glasgow coma score on admission and the most severely injured children had the lowest percentage of whole body energy expenditure accounted for by the brain, regardless of the age of the child. An alternative explanation for the lack of relation between systemic catecholamines and CMRO₂ may, therefore, be an impaired ability for neural and glial cells to utilise O₂ after trauma.

The weak but significant positive relation between CMRO₂ and plasma T₃ concentration is interesting. Although T₃ has been found to stimulate O₂ consumption in many tissues, it has previously been shown in animal models to have a minimal effect on brain tissue. This has always been perplexing because of the large numbers of T₃ receptors within the brain and has been explained by the proposal that T₃ has other metabolic effects within the brain. These influences include effects on adrenergic receptors and stimulation of synthesis of nerve growth factor, both of which are potentially important in traumatic encephalopathy. It is interesting to speculate that T₃ may stimulate O₂ consumption in some cell types within the brain in unusual circumstances, such as trauma, giving rise to the positive relation found.

In conclusion, after severe head injury there was no evidence for a positive relation between the metabolic rate of the brain and the rest of the body. Although BVOC was influenced by the whole body stress response to injury, there was no evidence of a similar effect on CMRO₂. It is not clear whether CMRO₂ and BVOC are positively related in health and this relation is then abolished after head injury or whether
CMRO₂ and BVO₂ are always determined independently. Studies to examine the relation between CMRO₂ and BVO₂ in health would be needed to resolve this issue.

The important clinical message of this study is that CMRO₂ needs to be measured directly after severe head injury and not inferred from measurements of whole body energy expenditure. Medical interventions aiming to reduce CMRO₂ after severe head injury in children need to be specific to the brain and it should not be assumed that measures which decrease whole body energy expenditure will necessarily have the same effect on CMRO₂.

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Appendix

As outlined in the regression coefficients of the metabolic rate of the whole body of the subject (0.160, 195% CI: 0.243 to 0.076) because the metabolic rate of the body is also calculated by subtracting CMRO₂ from the metabolic rate of the whole body, thereby reducing a bias. Determining the amount of this bias is not straightforward and depends on assumptions, the values of which are not known with any certainty: a heuristic approach to this problem is outlined below.

Suppose the true total cerebral, whole body, and residual metabolic rates of an individual are denoted by X, Y, and Z = X - Y. The observed total cerebral and whole body metabolic rates are x = X + εₓ, and y = Y + εᵧ. εₓ and εᵧ are measurement errors with variances δₓ and δᵧ respectively. If we assume the regression of X on Z has coefficient β, then if the metabolic rates of the brain and the rest of the body are unrelated, β = 0. The observation regression coefficient of x on z = y - x will not be β but

\[
\delta \left( \frac{\delta_x - \delta_y}{\delta_x} \right) - \frac{\delta_x}{\delta_y} + \frac{\delta_y}{\delta_x} = \delta_z
\]

where δᵢ is the variance of i. Separate analyses suggested reasonable values for δₓ and δᵧ of 0.6 and 0.025. The variance of the error in total CMRO₂ is less well known, but a reasonable value is between 0.05 and 0.15. Taking δᵢ = 0 and inverting the above expression gives an adjusted estimate of 0.10 with corresponding interval estimate (-0.091 to 0.110). Varying δᵢ from 0.05 to 0.15 gives similarly equivocal interval estimates.


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**NEUROLOGICAL STAMP**

*Convallari majalis* (lily of the valley)  
(also known as Our Lady’s tears, ladder to heaven)

Herbalists as far back as the 16th century recommended the blossoms of the lily of the valley soaked in wine for strengthening the memory and soothing inflamed eyes. Soaked in water it was said to ease gout. These remedies (called golden water) were so highly valued that they were stored in gold or silver vessels. Another of the age old uses of the plant was for treatment of heart ailments. Like fox-glove, the plant strengthens the heart beats although its effects are milder.

Subject to many legends its white flowers became a symbol of the Virgin Mary, was called Our Lady’s tears, and appeared in many paintings of the Virgin. The even, step-like, arrangements of the flowers along the stalk inspired medieval monks to name the plant ladder to heaven; and its fragrance was said to attract nightingales.

Lily of the valley is shown here on a stamp issued by Bulgaria in 1968 (Stanley Gibbons 1853, Scott 1730) illustrating medicinal plants and herbs.

L F HAAS
Changes in cerebral oxygen consumption are independent of changes in body oxygen consumption after severe head injury in childhood.

D S Matthews, J N Matthews, A Aynsley-Green, R E Bullock and J A Eyre

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