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.

(Keywords: children; head injury; energy metabolism)

Cerebral O₂ consumption (CMRO₂) accounts for about 20% of total body oxygen consumption in healthy resting adults. 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, 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. Robertson et al have shown a similar decrease in whole body O₂ consumption (V̇O₂) over time in adults with severe head injury. 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 V̇O₂, 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 hyperperfusion 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. 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. 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. In children aged less than 4 years, the adaptation of the Glasgow coma score described by James and Trauner was used. 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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<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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<td>8-8</td>
<td>M</td>
<td>3</td>
<td>f2-3, m 45-180</td>
<td>79</td>
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<td>10</td>
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<tr>
<td>15-6</td>
<td>F</td>
<td>3</td>
<td>f0-9, m 40-75</td>
<td>10</td>
<td>2</td>
<td>35</td>
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<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>
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<tr>
<td>14-0</td>
<td>M</td>
<td>4</td>
<td>f2-5-3-8</td>
<td>178</td>
<td>11</td>
<td>10</td>
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<td>8-4</td>
<td>M</td>
<td>6</td>
<td>f1-6-6, m 130-310</td>
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<td>9</td>
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<tr>
<td>6-4</td>
<td>F</td>
<td>6*</td>
<td>f2-6-4, m 80</td>
<td>55</td>
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<tr>
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<td>9-9</td>
<td>M</td>
<td>8</td>
<td>f2-5-5, m 50-100</td>
<td>28</td>
<td>4</td>
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</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.
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 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 0–6–0–80 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:

\[ O_2 \text{ content} = \frac{Hb \times O_2 \text{ sat}^\circ \times 1.39 + (0.023 \times P_O_2)}{100} \]

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:

\[ \text{CMRO}_2 = \text{CBF} \times (A - V) \]

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 cerebrovascular 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-cerebrovascular 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 only about 1% 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 5 l 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-
Changes in cerebral oxygen consumption are independent of changes in body oxygen consumption after severe head injury in childhood

Changes in cerebral oxygen consumption are independent of changes in body oxygen consumption after severe head injury in childhood. To compare CMRO₂ with the rest of the body, a measure of body O₂ consumption independent of brain was needed. To derive this, a measure of the brain's total O₂ consumption was needed. Thus an estimate of brain weight was required for each child. Brain weight was estimated from the head circumference measured when any scalp or soft tissue swelling had resolved using the equation described by Winnick and Rosso.

Total brain weight (kg) = \((HC - 20.5)^2 + 109.75\)

where HC = head circumference in cm.

The original equation was derived from measurements of head circumference of infants up to 1 year of age. To ascertain the predictive accuracy of the equation in older children, head circumference and brain weight were measured at postmortem in 10 adults less than 60 years of age dying from non-neurological causes, the formula applied to the data, and the results analysed. Brain weight was found to be estimated with an accuracy of ±5%.

Body oxygen consumption independent of brain (BVO₂) was calculated according to the equation:

\[ BVO₂ = \frac{VO₂ - (CMRO₂ \times BW)}{FFM - BW} \]

where \(VO₂\) = total whole body oxygen consumption (mmol.min⁻¹); \(CMRO₂\) = cerebral oxygen consumption (mmol.kg brain⁻¹.min⁻¹); \(BW\) = estimated brain weight (kg); \(FFM\) = fat free mass (kg)

The BVO₂ 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 models18 fitted using the ML3 program.19 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.

**CALCULATION OF BODY O₂ CONSUMPTION INDEPENDENT OF CMRO₂**

The \(VO₂\) includes CMRO₂, which may account for up to 34% of total \(O₂\) consumption. To calculate \(CMRO₂\) with the rest of the body, a measure of body \(O₂\) consumption independent of brain was needed. To derive this, a measure of the brain's total \(O₂\) consumption was needed. Thus an estimate of brain weight was required for each child. Brain weight was estimated from the head circumference measured when any scalp or soft tissue swelling had resolved using the equation described by Winnick and Rosso.

The complete indirect calorimetry system was evaluated with \(N₂\) and \(CO₂\) dilution techniques as described by Westenskow et al.13 At an \(FiO₂\) of 0·3, the mean \(VO₂\) recovery was 99.9% (SD 2%).

**CALCULATIONS**

The \(VO₂\) was calculated from the equation:

\[ VO₂ = VE \left( \frac{(1 - FeO₂ - FeCO₂)}{FiO₂} \times FiO₂ - FeO₂ \right) \]

(using Haldane transformation)

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 biocomputer impedance, measured with a Holtain body composition analyser (Holain Ltd, Crosswell, Dyfed) and the child's height and age. Fat free mass was calculated from the equations of Schaefer et al.14

**MEASUREMENT OF PLASMA HORMONE CONCENTRATIONS**

A 2 ml blood sample was taken from the indwelling peripheral arterial catheter at the end of each measurement of \(VO₂\). Blood for plasma glucagon assay was collected into a tube containing aprotilin and the remaining sample was collected into a heparinised tube. Sample tubes were stored on ice during collection and plasma for hormone assays was immediately separated and stored at −80°C. Plasma T3 and glucagon concentrations were determined by radioimmunoassay15 and plasma adrenaline concentrations were determined by a double isotope radioenzymatic method.16

**REFERENCES**

5. aprotilin.
6. T3.
7. glucagon.
8. adrenaline.
10. Double isotope radioenzymatic method.
**Results**

A total of 79 serial measurements of VO$_2$, CMRO$_2$, consumption, and plasma hormone concentrations were made in 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.
Changes in cerebral oxygen consumption are independent of changes in body oxygen consumption after severe head injury in childhood

flow and there was evidence of absolute hypoaemia in only one measurement.

Initial values of CMRO\textsubscript{2} 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 BVo\textsubscript{2} per kg fat free mass over the first 120 hours after the head injury. There was a significant fall in BVo\textsubscript{2} from mean 0.30 mmol.kg\textsuperscript{-1}.min\textsuperscript{-1} at a mean of 12 hours to mean 0.26 mmol.kg\textsuperscript{-1}.min\textsuperscript{-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 BVo\textsubscript{2} 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 O\textsubscript{2} consumption as a percentage of Vo\textsubscript{2}(CMRO\textsubscript{2}/Vo\textsubscript{2}) over the first 120 hours after the head injury. The total CMRO\textsubscript{2} accounted for a mean of 17% Vo\textsubscript{2} with a wide range of 5–34%.

There was no evidence of a significant change of the percentage of Vo\textsubscript{2} accounted for by CMRO\textsubscript{2} 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 Vo\textsubscript{2} accounted for by CMRO\textsubscript{2} on admission and Glasgow coma score (P = 0.007, r = 0.73). As the percentage of Vo\textsubscript{2} accounted for by CMRO\textsubscript{2} may change with age, the effect of age on the relation was analysed by multiple regression. The significant positive relation between CMRO\textsubscript{2}/Vo\textsubscript{2} 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 CMRO\textsubscript{2} and BVo\textsubscript{2}. Analysis of the raw data showed an apparent negative relation between CMRO\textsubscript{2} and BVo\textsubscript{2} (regression coefficient = −0.16, 95% CI −0.24 to −0.08)

![Figure 2: Within-child relation between BVo\textsubscript{2} and possible mediators. Each graph shows the residuals from the mean for BVo\textsubscript{2} and each possible mediator. (A) log\textsubscript{10} adrenaline, (B) T3, and (C) glucagon.](image-url)
but there are statistical problems interpreting this regression as \( BV_0 \) 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 BV0\(_2\).

The CMRO\(_2\) and BV0\(_2\) 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 ketones \( \beta \)-hydroxybutyrate and acetocacetate 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:

\[
RQ_{\text{total}} = \lambda RQ_{\text{brain}} + (1 - \lambda) RQ_{\text{body}}
\]

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.

**WITHIN CHILD RELATION BETWEEN BODY O\(_2\) CONSUMPTION INDEPENDENT OF BRAIN AND POSSIBLE MEDIATORS**

Using multilevel modelling, log adrenaline, T3, and glucagon were all found to have inde-

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

365

Dependent significant relations with whole body energy expenditure in a previous study. Thus the relation of these variables with BVo₂ and CMRo₂ were analysed.

Figure 2 shows the within-child relations between BVo₂ and possible mediators. With multilevel modelling, significant positive relations were found between BVo₂ and log adrenaline (P = 0.0002), T₃ (P = 0.017), and glucagon (P = 0.005). Table 2 shows further details of the results of the statistical analysis.

**Within Child Relation Between Cerebral O₂ Consumption and Possible Mediators**

Figure 3 shows the within-child relations between CMRo₂ and possible mediators. Using multilevel modelling, a significant positive relation was found between CMRo₂ and T₃ (P = 0.023). There was no evidence of a relation between CMRo₂ and log adrenaline (P = 0.887) or glucagon (P = 0.18). Table 2 gives further details of the results of the statistical analysis.

**Discussion**

In our study there was no evidence of a positive relationship between CMRo₂ and BVo₂ 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 BVo₂ 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 BVo₂, thus reducing the likelihood of finding a close positive relation between CMRo₂ and BVo₂.

In our study, the hormonal mediators shown to have a stimulatory effect on BVo₂ were adrenaline, T₃, and glucagon. The positive effects of the hormones on BVo₂ 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 BVo₂, 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 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 BVo₂ 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 BVo₂ 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 there is a statistical problem in interpretation of the regression coefficient of the metabolic rate of the rest of the body when it is related to total CMRO₂: (−0.010±0.006, 95% CI 0.243 to 0.076) because the metabolic rate of the rest of the body must be calculated by subtracting CMRO₂ from the metabolic rate of the whole body, thereby creating a negative bias. Determining the amount of this bias is not straightforward and depends on quantities, 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 resting metabolic rates of an individual are denoted by X, Y, and Z = Y − X. The observed total cerebral and whole body metabolic rates are x = X + ε₁ and y = Y + ε₂, where ε₁ and ε₂ are measurement errors with variances δ₁ and δ₂ 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 observed regression coefficient of x on z = y − x will not be β but

\[ \beta - \begin{cases} \delta_1 & \text{if } \delta_1 > 0.15 \text{ and } \delta_2 > 0.15 \text{, assumes equally interval estimates.} \end{cases} \]

where \( \sigma^2 \) is the variance of \( \sigma_z \). Separate analyses suggested reasonable values for \( \sigma^2 \) and \( \delta_1 \) 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 \( \delta_1 = 0 \) and inverting the above expression gives an adjusted estimate of 0.010 with corresponding interval estimate (−0.091 to 0.110). Varying \( \delta_1 \) from 0.05 to 0.15 gives similarly equivocal interval estimates.

14 Schaefer F, Georgi M, Ziegler A, Schrader K. Usefulness of brain arayahgol additional support from the Intensive Care Society, the Buttle Trust, The Mason Medical Foundation, the Peel Medical Research Trust, and CHILD.

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


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 foxglove, 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