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EDITORIAL

Biochemical markers of cerebral damage

There was a considerable incidence of post-operative stroke and neurological complications during 1992 to 1993 in England, Wales and Northern Ireland [1]. While intensive haemodynamic monitoring may reduce the rate of reinfarction and cardiac death in patients with recent myocardial infarction [2], the usefulness of perioperative monitoring of cerebral function is less well established: it is possible that improved monitoring of cerebral sufficiency could reduce the incidence or effects of post-operative neurological complications and strokes.

Intra-operative cerebral monitoring

Currently, cerebral monitoring measures either the results of the balance between cerebral oxygen supply and demand, or cerebral blood flow directly. However, neuropsychological testing is the gold standard for assessing cerebral damage, and the effectiveness of a cerebral monitor should be validated against this.

Monitors of cerebral oxygen supply/demand

The electroencephalogram (EEG) is generated by the pyramidal cells in the cortex. EEG abnormalities associated with the production of cerebral ischaemia [3] are well correlated with reductions in cerebral blood flow (CBF) demonstrated by ^{133}Xe. At a normal cerebral metabolic rate for oxygen ($CMRO_2$) in anaesthetized patients, the flow required to maintain a normal EEG (critical CBF), is 30% (15 mL 100 g^{-1} min^{-1}) of normal flow (50 mL 100 g^{-1} min^{-1}) and lower flows usually cause EEG changes. Changes in the EEG are always produced rapidly when the flow is reduced to less than 10 mL 100 g^{-1} min^{-1} (ischaemic flow) [4]. Ultimately the EEG becomes isoelectric but this may not indicate that there is irreversible damage of the cortex [5]. However, anaesthetic techniques and hypothermia [6] may also produce a flat EEG that is indistinguishable from global ischaemia. Artifacts as a result of diathermy and other electrical equipment may mimic normal electrical activity in the presence of an ischaemic (flat) EEG.

Despite these drawbacks, the EEG has proved to be a sensitive means of monitoring neurological function up to 1 day post-operatively. In 1145 consecutive carotid endarterectomies all patients with a prolonged or fixed neurological deficit had an associated EEG abnormality [4]. However, with follow-up extending to 6 years, the EEG was an unreliable indicator of the adequacy of cerebral perfusion [7] when used to determine whether a temporary shunt was needed during carotid endarterectomy.

The Cerebral Function Analysing Monitor (CFAM) provides easily interpreted processed EEG data by analysing the EEG amplitude and frequency distribution [8]. However, it is recommended that the CFAM be combined with serial conventional EEG recording in order to improve reliability when monitoring cortical areas [9].

Near infra-red spectroscopy (NIRS) is well established for studying cerebral oxygenation and haemodynamic responses in neonates [10,11] using 'transmission spectroscopy', where light is shone across the whole head. In adults, because of the large head and thick skull 'reflectance spectroscopy' is required with the optodes a few centimetres apart on the same side of the head [12]. With wide (>4 cm) optode separations, NIRS measures true cerebral oxygenation, but it is also affected significantly by changes in extracranial blood flow and oxygenation [13]. Further work is necessary to define those situations in which cerebral oximetric monitoring is useful, valid and reliable.

Monitors of CBF

CBF measurements supplement, but are not a substitute for, a continuous monitor of cerebral function.

Transcranial Doppler (TCD) is usually applied over the middle cerebral artery and provides continuous

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information on blood flow velocity [14]. As the diameter of the large cerebral arteries does not alter in the absence of vasospasm, changes in middle cerebral artery velocity (MCAV) reflect changes in blood flow to the majority of the cerebral cortex on that side. However, the changes in MCAV correlate neither with other cerebral monitoring findings nor with clinical neurological deficits [15].

Regional cerebral blood flow can be determined from clearance curves obtained from extracranial detection of intra-arterially injected ^{133}Xe [16]. While CBF with ^{133}Xe shows a good correlation with EEG abnormalities, the severity of ischaemia indicated by ^{133}Xe clearance does not predict the appearance of neurological complications. Indeed, during carotid occlusion the higher the CBF the more likely that patients developing EEG changes would develop neurological complications [3].

These intra-operative cerebral monitors (EEG, CFAM, NIRS, TCD, CBF measurement) can be quite sensitive to cerebral ischaemia, but have poor specificity. They are also of limited value for post-operative assessment and follow-up. Furthermore, these monitors have not been sufficiently validated against neuropsychological testing – the gold standard for assessing mild global cerebral damage.

Neuropsychological testing

Neuropsychological impairment as an indicator of irreversible brain dysfunction has formed the basis for granting disability pensions [17] and neuropsychological tests have also been used to evaluate the fitness of patients to return to driving after cerebral damage [18]. While major stroke and neurologic abnormalities can be diagnosed rapidly on recovery from anaesthesia, more subtle defects require neuropsychological testing, which is usually carried out 8 weeks after operation to avoid the residual effects of anaesthesia and surgery. In the evaluation of the effects of carotid endarterectomy, cognitive improvement is greater in functions ipsilateral to the operation [19], and the neuropsychological tests used must be designed appropriately.

Biochemical markers

Subtle cerebral defects can be diagnosed by neuropsychological testing, but this can only be used for late-stage assessment. The development of techniques to identify biochemical markers of cerebral damage offers the possibility of rapid, continuous and specific diagnosis of cerebral ischaemia which would allow the early institution of neuroprotective therapies.

Lactate

Studies have shown that high concentrations of CSF lactate correlate with rising intracranial pressure, increasing cerebral arterial spasm and cerebral oedema following stroke and subarachnoid haemorrhage [20, 21]. CSF lactate values above 3.5 mmol L^{-1} are associated with a poor prognosis [21], while values below 2.5 mmol L^{-1} indicate a good chance of survival [20]. However, arterial and jugular bulb blood lactate concentrations are not helpful [22]. CSF lactate can easily be contaminated with lactate from shed blood cells [21] and it is also affected by CSF glucose levels [22,23]. Hence, lactate levels may not represent permanent cerebral cell damage [24,25] and are not closely and specifically correlated to the clinical outcome [26].

Creatine kinase and others

In contrast to brain lactate level, the loss of large molecular cytosolic enzymes from the brain cells and their increase in body fluid compartments have been used as indices of irreversible brain cell damage. The sensitivity of brain-specific creatine kinase (CK-BB) for cerebral damage is affected by the type of cerebral insult. CSF CK-BB seems to be an early indicator of brain damage and its level reflects the extent of cerebral damage following externally inflicted head injuries [27]. In the study of Vaagenes *et al.* [24], leakage of brain cytosolic CK-BB into the CSF strongly suggested irreversible brain damage after induced cardiac arrest followed by cardiopulmonary resuscitation. The initial change was a decrease in brain tissue CK-BB. After 24 h, CSF CK-BB increased with a peak at 48 h and returned to normal by 96 h. Peak CK-BB levels correlated with histopathological cerebral damage and neurological deficit score at 96 h. In comatose states following cardiac arrest, CSF CK-BB peaks of more than 50 U L^{-1} at 48 h in dogs [24], and of more than 10–20 U L^{-1} at 48–72 h in patients [28],

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show a strong correlation with permanent brain damage. However, blood levels of CK-BB are not reliable for predicting brain damage after cardiac arrest [29] because CK-BB may also be released from extracerebral sources [30]. In addition, CSF CK-BB values are not predictive for stroke [31,32] and are easily inactivated at body temperature [33]. This lack of thermostability prevents the use of CK-BB for comparing 'warm' cardiopulmonary bypass with 'cold' bypass. Lactate dehydrogenase (LD) and aspartate aminotransferase (ASAT) are more thermostable [33] but there is no good correlation between their CSF levels and neurological deficit after cardiac arrest [24] and they are also unpredictive for stroke [31,32].

Neurone-specific enolase and S-100

Neurone-Specific Enolase (NSE) is the gamma-subunit of enolase present primarily in the cytoplasm of neurones. In cerebral reperfusion injury, the formation of oxygen free radicals following the reduction of oxygen to superoxide radicals reduces membrane integrity and results in leakage of NSE from the cytosol into the extracellular space [34,35] and then into plasma. S-100 protein is a calcium-binding dimeric protein with α and β subunits where the β-subunit is highly brain specific and found predominantly in glial cells [36], and is similarly found in plasma following cerebral cell damage. The availability of a radioimmune assay for NSE and the recent development of the S-100 assay for the $\beta\beta$ and $\alpha\beta$ isoforms (Sangtec S-100), has offered a rapid, specific and semi-quantitative test for cerebral neuronal and glial cell damage. NSE and S-100 protein are thermostable and their assay is not affected by heparin or protamine. Therefore, samples can be taken throughout surgery involving cardiopulmonary bypass. Haemolysis has a marked effect on measured NSE, but none on S-100. Correction of NSE assays should be made for visible amounts of haemolysis [unpublished data].

Animal data

The kinetics of S-100 and NSE concentrations in rat CSF are significantly affected by the type and duration of injury and the degree of ischaemia. Traumatic cortical contusion was followed by a rapid increase in both S-100 and NSE and a peak level occurred in both after about $7\frac{1}{2}$ h, after which the values declined toward normal. The increase and decrease in S-100 and NSE levels were slower after focal cerebral ischaemia induced by middle cerebral artery occlusion with a peak after 2–4 days. S-100 was generally higher than NSE after trauma [37] implying more severe damage to glial cells than to neurones, whereas after middle cerebral artery occlusion NSE concentrations were higher than S-100 values. NSE levels correlated well with the number of cerebral artery occlusions and their duration [38].

Serum or plasma samples have been used in animal and human studies [35,39] but it is likely that CSF samples are more predictive [40–42] as there would be a time delay of NSE and S-100 release measured in plasma compared with that measured in CSF because of effect of the blood brain barrier.

Human data

NSE and S-100 have been used in humans as sensitive markers of brain injury after stroke [43], hypoxic ischaemic brain damage, coma following cardiac arrest [40–41] and acute seizure activity [42]. Both markers have also been used as prognostic indicators of clinical outcome in cerebrovascular diseases [39] and in asphysic full-term new-borns [44]. Pathologically high CSF levels of NSE were found 24 h after coronary artery bypass grafting in 95% of the patients. All S-100 protein concentrations were within the normal range. Post-operative levels of these two biochemical markers in the CSF tended to be lowest in the flat-sheet membrane oxygenator group during cardiopulmonary bypass surgery [45].

However, questions remain about the timing of the release of NSE and S-100 following cerebral damage, and their predictive accuracy following surgery needs to be established against neuropsychological testing as the gold standard for assessing cerebral damage.

Summary

Neuroprotective therapy is likely to be most effective in preventing or minimizing the effects of cerebral ischaemia when given as early as possible after the insult. Neuropsychological testing is the gold standard for assessing minor cerebral damage, but is carried out several days or weeks after surgery and is too

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late to be useful for instituting therapy. Current intraoperative cerebral monitors (EEG, CFAM, NIRS and TCD) can detect cerebral ischaemia with good sensitivity, and give immediate results, but their specificity for ischaemia is low. Biochemical markers offer the possibility of rapid and specific diagnosis of cerebral ischaemia which would allow the early institution of neuroprotective therapies.

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References

1 Campling EA, Devlin HB, Hoile RW, Lunn JN. 1995 *The Report of the National Confidential Enquiry into Perioperative Deaths 1992/1993 NCEPOD London.*
2 Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infraction. *Anesthesiology* 1983; **59**: 499–505.
3 Zampella E, Morawetz RB, McDowell HA, Zeiger HE, Varner PD, McKay RD. The importance of cerebral ischemia during carotid endarterectomy. *Neurosurgery* 1991; **29**: 727–731.
4 Sundt TM, Sharbrough FW, Piepgras DG, Kearns TP, Messick Jr JM, O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy with results of surgery and hemodynamics of cerebral ischemia. *Mayo Clin Proc* 1981; **56**: 533–543.
5 Cabral R, Prior PF, Scott DF, Brierley B. Reversible profound depression of cerebral electrical activity in hyperthermia. *Electroencephalogr Clin Neurophysiol* 1977; **42**: 697–701.
6 Picard L, Braun M, Anxionnat R, Claise B, Ducrocq X, Pincemaille B. Venous angiography: importance in the diagnosis of brain death. 125 cases. *Bull Acad Natl Med* 1995; **179**: 27–40.
7 Rosenthal D, Stanton Jr PE, Lamis PA. Carotid endarterectomy. The unreliability of intraoperative monitoring in patients having stroke or reversible ischaemic neurological deficit. *Arch Surg* 1981; **116**: 1569–1575.
8 Sebel PS, Maynard DE, Major E, Frank M. The cerebral function analysing monitor. A new microprocessor-based device for the on-line analysis of the EEG and evoked potentials. *Br J Anaesth* 1983; **55**: 1265–1270.
9 Tasker RC, Boyd SG, Harden A, Matthew DJ. The cerebral function analysing monitor in paediatric medical intensive care: applications and limitations. *Intensive Care Med* 1990; **16**: 60–68.
10 Edwards AD, Wyatt JS, Richardson C, Delpy DT, Cope M, Reynolds EO. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet* 1988; **2**: 770–771.
11 Brazy JE, Lewis DV, Mitnick MH, Jobsis van der Vliet FF. Noninvasive monitoring of cerebral oxygenation in preterm infants: preliminary observations. *Pediatrics* 1985; **75**: 217–225.
12 Harris DNF. Editorial – Near infra-red spectroscopy. *Anaesthesia* 1995; **50**: 1015–1016.
13 Germon TJ, Kane NM, Manara AR, Nelson RJ. Near-infrared spectroscopy in adults: effects of extracranial ischaemia and intracranial hypoxia on estimation of cerebral oxygenation. *Br J Anaesth* 1994; **73**: 503–506.
14 Naylor AR, Whyman MR, Wildsmith JA, McClure JH, Jenkins AM, Merrick MV. Factors influencing the hyperaemic response after carotid endarterectomy. *Br J Surg* 1993; **80**: 1523–1527.
15 Naylor AR, Whyman M, Wildsmith JA, McClure JH, Jenkins AM, Merrick MV. Immediate effects of carotid clamp release on middle cerebral artery blood flow velocity during carotid endarterectomy. *Eur J Vasc Surg* 1993; **7**: 308–316.
16 Sundt Jr TM, Sharbrough FW, Anderson RE, Michenfelder JD. Cerebral blood flow measurements and electroencephalograms during carotid endarterectomy. *J Neurosurg* 1974; **41**: 310–320.
17 Perrild H, Hansen JM, Arnung K, Olsen PZ, Danielsen U. Intellectual impairment after hyperthyroidism. *Acta Endocrinologica Copenhagen* 1986; **112**: 185–191.
18 Galski T, Bruno RL, Ehle HT. Driving after cerebral damage: a model with implications for evaluation. *Am J Occup Ther* 1992; **46**: 324–332.
19 Mononen H, Lepojarvi M, Kallanranta T. Early neuropsychological outcome after carotid endarterectomy. *Eur Neurol* 1990; **30**: 328–333.
20 Busse O. Prognosis of cerebral ischemia. Significance of the cerebrospinal fluid lactate level and computer tomographic findings. *Fortschritte der Medizin* 1982; **110**: 1197–1200.
21 Voldby B, Enevoldsen EM. Intracranial pressure changes following aneurysm rupture. Part 2: associated cerebrospinal fluid lactacidosis. *J Neurosurg* 1982; **56**: 197–204.
22 De-Salles AA, Muizelaar JP, Young HF. Hyperglycemia, cerebrospinal fluid lactic acidosis, and cerebral blood flow in severely head-injured patients. *Neurosurgery* 1987; **21**: 45–50.
23 Natale JE, Stante SM, D'Alecy LG. Elevated brain lactate accumulation and increased neurologic deficit are associated with modest hyperglycemia in global brain ischemia. *Resuscitation* 1990; **19**: 271–289.
24 Vaagenes P, Safar P, Diven W, Moossy J, Rao G, Cantadore R. Brain enzyme levels in CSF after cardiac arrest and resuscitation in dogs: markers of damage and predictors of outcome. *J Cereb Blood Flow Metab* 1988; **8**: 262–275.

https://doi.org/10.1046/j.1365-2346.1997.d01-620.x Published online by Cambridge University Press

25 Gramham DI. The pathology of brain ischemia and possibilities for therapeutic intervention. *Br J Anaesth* 1985; **57**: 1–17.
26 Terent A, Ronquist G. Cerebrospinal fluid markers of disturbed brain cell metabolism in patients with stroke and global cerebral ischemia. *Acta Neurol Scand* 1980; **62**: 327–335.
27 Anagnostopoulos DI, Dontas IA, Kotsarelis DV, Julien G, Karayannacos PE, Diakolios CE. Creatine kinase (CK-BB) determination in cerebrospinal fluid after acute experimental head injury. *Br J Neurosurg* 1988; **2**: 169–72.
28 Vaagenes P, Kjekshus TK, Torvik A. The relationship between cerebrospinal fluid creatine kinase and morphological changes in the brain after transient cardiac arrest. *Circulation* 1980; **61**: 1194–1199.
29 Longstreth T, Clayson KJ, Sumi SM. Cerebrospinal fluid and serum creatine kinase BB activity after out-of-hospital cardiac arrest. *Neurology* 1981; **31**: 455–458.
30 Zarghami N, Yu H, Diamondis EP, Sutherland DJ. Quantification of creatine kinase BB isoenzyme in tumor cytosols and serum with an ultrasensitive time-resolved immunofluoromeric technique. *Clinica Biochemistry* 1995; **28**: 243–253.
31 Sherwin AL, Norres FW, Bulche JA. Spinal fluid creatine kinase in neurological disease. *Neurology* 1969; **19**: 993–999.
32 Vaagenes P, Urdal P, Melvoll R, Valnes K. Enzyme level changes in the cerebral spinal fluid of patients with acute stroke. *Arch Neurol* 1986; **43**: 357–362.
33 Vaagenes P. Effects of therapeutic hypothermia on activity of some enzymes in cerebrospinal fluid of patients with anoxic-ischemic brain injury. *Clin Chem* 1986; **32**: 1336–1340.
34 Gruener N, Gross B, Gozlan O, Barak M. Increase in superoxide dismutase after cerebrovascular accident. *Life Sciences* 1994; **54**: 711–713.
35 Barone FC, Clarke RK, Price WJ, White RF, Feuerstein GZ, Storer BL. NSE increases in cerebral and systemic circulation following focal ischemia. *Brain Res* 1993; **623**: 77–82.
36 Allore R, O'Hanlon D, Price R, Neilson K. Gene encoding the beta subunit of S-100 protein is on chromosome 21: implications for Down syndrome. *Science* 1988; **11**: 1311–1313.
37 Hardemark HG, Ericsson N, Kotwica, Rundstrom G, Mendel Hartvig I, Olsson Y. S-100 protein and neuron-specific enolase in CSF after experimental traumatic or focal ischemic brain damage. *J Neurosurg* 1989; **71**: 727–731.
38 Steinberg R, Gueniau C, Scarna H, Keller A, Worcel M, Pujol JF. Experimental brain ischemia: neuron-specific enolase level in cerebrospinal fluid as an index of neuronal damage. *J Neurochem* 1984; **43**: 19–24.
39 Schaarschmidt H, Prange HW, Reiber H. Neuron-specific enolase concentrations in blood as a prognostic parameter in cerebrovascular diseases. *Stroke* 1994; **25**: 558–565.
40 Usui A, Kato K, Murase M, Hotta T, Tanaka M, Takeuchi E. Neural tissue-related protein (NSE, GO alpha, 28-kDa calbindin-D, S-100b and CK-BB) in serum and CSF after cardiac arrest. *J Neurol Sci* 1994; **123**: 134–139.
41 Karkela J, Bock E, Kaukinen S. CSF and serum brain-specific creatine kinase isoenzyme (CK-BB), neuron-specific enolase (NSE) and neural cell adhesion molecule (NCAM), as prognostic markers for hypoxic brain injury after cardiac arrest in man. *J Neurol Sci* 1993; **116**: 100–109.
42 Rabinowicz AL, Correale JD, Couldwell WT, DeGiorgio CM. CSF neuron-specific enolase after methohexital activation during electrocorticography. *Neurology* 1994; **44**: 1167–1169.
43 Persson L, Hardemark HG, Gustafsson J, Rundstrom G, Mendel Hartvig I, Esscher T. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of all damage in human central nervous system. *Stroke* 1987; **18**: 911–918.
44 Garcia-Alix A, Cabanas F, Pellicer A, Hernanz A, Stiris TA, Quero J. NSE and myelin basic protein: relationship of CSF concentrations to the neurologic condition of asphyxiated full-term infants. *Pediatrics* 1994; **93**: 234–240.
45 Sellman M, Ivert T, Ronquist G, Caesarini K, Persson L, Semb BK. Central nervous system damage during cardiac surgery assessed by 3 different biochemical markers in cerebrospinal fluid. *Scand Thorac Cardiovasc Surg* 1992; **26**: 39–45.

https://doi.org/10.1046/j.1365-2346.1997.d01-620.x Published online by Cambridge University Press