Burst suppression or isoelectric encephalogram for cerebral protection: evidence from metabolic suppression studies

P. W. Doyle¹ and B. F. Matta² *

¹Department of Anaesthesia, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR, UK.
²Department of Anaesthesia, Addenbrooke's Hospital, Box 93, Hills Road, Cambridge CB2 2QQ, UK
*Corresponding author

Metabolic suppression may have a role in cerebral protection. It is often assumed that the cerebral metabolic and protective effects of qualitative burst suppression are similar to those of the isoelectric encephalogram (EEG). We have examined the effect of different degrees of EEG suppression on blood flow and oxygen difference during general anaesthesia. We studied 11 patients undergoing general anaesthesia for resection of acoustic neuromas. The study was performed after surgery with propofol and remifentanil anaesthesia. Transcranial Doppler ultrasonography and jugular bulb venous saturations were measured at values of EEG suppression: 0%, 50% and 100% (isoelectric EEG). Data from nine patients were suitable for analysis. There were no significant differences in mean arterial pressure, heart rate or $P_{aCO_2}$ during EEG activity, 50% burst suppression ratio or isoelectric EEG. There was a significant decrease in middle cerebral artery flow velocity ($v_{mca}$) with increasing EEG suppression (0% suppression, mean 38 (SEM 4) cm s⁻¹; 50% suppression, 29 (3) cm s⁻¹; and 100% suppression, 24 (2) cm s⁻¹; P<0.05). Jugular bulb venous saturations did not change consistently with the change in EEG activity, indicating intact flow–metabolism coupling. We conclude that the degree of EEG suppression had a significant effect on blood flow. If flow–metabolism coupling is maintained, the assumption that cerebral metabolism during 50% EEG burst suppression is equivalent to isoelectric EEG may not be justified. If cerebral protection is related to brain metabolism, then an isoelectric EEG may give more cerebral protection than 50% burst suppression.

Br J Anaesth 1999; 83: 580–4

Keywords: brain, metabolism; measurement techniques, electroencephalography; measurement techniques, Doppler ultrasonography; measurement techniques, oximetry

Accepted for publication: May 7, 1999

Cerebral protection before, and cerebral resuscitation after, cerebral damage have been intensive areas of research for the past 25 yr. Despite advances in understanding the processes underlying cerebral damage, there has been surprisingly little translation from experimental to clinical practice in terms of improved outcome as a result of administering brain protective agents.¹ Simple manoeuvres such as normoxia and maintenance of optimal cerebral perfusion pressure remain the mainstay of treatment.² In addition to anti-inflammatory agents, free radical scavengers, hypothermia and electrolyte channel blockers, cerebral protection is thought possible by metabolic suppression. Maximal reduction in cerebral metabolic rate (CMR) in animals has been achieved with the onset of electroencephalographic (EEG) isoelectricity.³ However, despite the lack of metabolic data in humans, it is commonly accepted that qualitative burst suppression is equivalent to EEG silence in terms of cerebral protection. In this study, we investigated if progressive EEG burst suppression decreased cerebral metabolism.

Patients and methods

The study was approved by the Cambridge Local Ethics Committee and written informed consent was obtained from all patients. We studied 11 patients (four males). All were undergoing general anaesthesia for resection of acoustic neuromas and the study was performed after surgery had been completed.

Patients received a standard anaesthetic which comprised infusions of propofol 6–10 mg kg⁻¹ h⁻¹ and atracurium 0.5 mg kg⁻¹ h⁻¹, and intermittent bolus doses of fentanyl 1–2 µg kg⁻¹, as required. The lungs were ventilated with oxygen and nitrous oxide. Routine monitoring consisted of electrocardiography, pulse oximetry, invasive arterial pressure, central venous pressure, oesophageal temperature
probes and right jugular bulb oximetry (Angiocath, Becton and Dickinson, USA).

During the operative procedure, body temperature was allowed to decrease spontaneously to 35°C. This was returned to 36–37°C before starting the study. Nitrous oxide administration was stopped approximately 30 min before the study and an oxygen–air mixture was used. The propofol infusion was continued and infusion of remifentanil at a rate of 0.1–0.4 µg kg⁻¹ min⁻¹ was given during the study. \( P_{\text{PaCO}_2} \) was adjusted (mean 4.8 (SEM 0.1) kPa) and mean arterial pressure (MAP) was maintained within 20% of baseline by infusion of 0.01% phenylephrine, as necessary.

Brain electrical activity was measured using a two-channel bipolar frontal montage (A-1000 EEG monitor, Aspect Medical Systems, MA, USA) which displayed unprocessed EEG (50 µV) and burst suppression ratio. The burst suppression ratio (BSR) quantifies burst suppression. To calculate BSR, suppression is recognized as those periods longer than 0.5 s during which EEG voltage is less than ±5 µV. Time in a suppressed state is measured and BSR is reported as the fraction of the epoch where the EEG is suppressed. Because of the variable (non-stationary) nature of burst suppression, BSR is averaged over at least 15 epochs (60 s).3 This has been an accepted method of EEG analysis since 1988.4 5 Burst suppression for perioperative use has been recommended in the two- or four-channel method7 and this is a common form of EEG analysis4. Ideally, 10- or 20-channel EEG electrode placement would be used, but when considering global metabolism, a bifrontal montage should reflect global EEG suppression. A burst suppression ratio of 100% implies EEG silence. The EEG electrodes were attached to the patient’s temporal areas and foreheads with self-preparing, low impedance electrodes (Zip electrodes, Aspect Medical Systems, MA, USA) and impedanc was confirmed as less than 10 000 W before measurements were made.

Cerebral blood velocity was measured by insonating the middle cerebral artery (MCA) ipsilateral to the jugular bulb catheter through the temporal window using a 2-MHz pulsed transcranial Doppler probe (DWL Multidop, Sipplingen, Germany). When the vessel was identified at a depth of 45–50 mm and the best signal possible was obtained, the probe was secured in position. Time-averaged flow velocity (vmca) was obtained by averaging maximal velocity over 4–5 cardiac cycles.8

During the study, increasing doses of propofol (mean 226 (range 142–476) µg kg⁻¹ min⁻¹) and remifentanil (0.2 (0.1–0.4) µg kg⁻¹ min⁻¹) were used to cause suppression of the EEG. With each patient serving as their own control, blood samples were obtained from the jugular venous bulb catheter (at no more than 2 ml min⁻¹) and radial artery for measurement of cerebral arteriovenous oxygen difference (A–V \( D_{O_2} \)) across the cerebral vessels at three states of stable BSR (i.e. 0%, 50% and 100% BSR or complete EEG silence). A–V \( D_{O_2} \) was calculated using the equation:

\[
A–V \ D_{O_2} = \text{arterial } O_2 \text{ content (C}\text{a}_{O_2}) – \text{jugular venous bulb } O_2 \text{ content (C}\text{j}_{O_2}) – \text{(Hgb} \times 1.39 \times \text{Sa}_{O_2} + 0.003 \times \text{Pa}_{O_2}) – \text{(Hgb} \times 1.39 \times \text{Sj}_{O_2} + 0.003 \times \text{Pj}_{O_2}).
\]

The study sequence was randomized to increasing or decreasing EEG activity (i.e. from 0% to 100% BSR or vice versa). vmca was also recorded at each level of EEG suppression.

Data were compared using ANOVA (statview 4.0 on a MacIntosh computer). \( P<0.05 \) was considered significant.

**Results**

Results from nine patients were analysed; two patients were withdrawn because of surgical complications. The main findings are shown in Tables 1 and 2.
There was no significant difference in MAP, \( P_{\text{ACO}_2} \), or heart rate during EEG activity, 50% BSR or EEG silence. All patients required infusion of phenylephrine to maintain MAP during the BSR and EEG silence parts of the study.

Although there was a significant decrease in \( \text{vmca} \) with decreasing EEG activity (mean \( \text{vmca} \) at 0% BSR, 38 (SEM 4) cm s\(^{-1}\); 50% BSR, 29 (3) cm s\(^{-1}\); and 100% BSR, 24 (2) cm s\(^{-1}\); \( P<0.05 \)), A–V \( D\text{O}_2 \) remained unchanged indicating intact flow–metabolism coupling.

**Discussion**

We found that in humans, cerebral blood flow during EEG silence appeared to be significantly less than that during 50% burst suppression. Reduction in EEG activity was associated with a significant reduction in \( \text{vmca} \) (\( P<0.05 \)), but a constant A–V \( D\text{O}_2 \), suggesting intact flow–metabolism coupling.

We used propofol as part of the anaesthetic technique to induce cerebral metabolic suppression. Propofol has been shown to be devoid of direct cerebral effects, with carbon dioxide reactivity and autoregulation remaining intact at high doses.\(^9\) Propofol reduces cerebral metabolism with a consensual reduction in EEG activity, oxygen consumption and cerebral blood flow (CBF).\(^10\)\(^11\) Its antioxidant properties may also be of benefit.\(^12\) It is known from previous studies that to induce an isoelectric EEG, high doses of propofol are required.\(^13\) Remifentanil was added to allow a propofol-sparing effect and because it has a very short context-sensitive half-life. Electroencephalography can measure only cortical and not subcortical activity, which accounts for approximately 40–50% of metabolism in an awake subject.

For transcranial Doppler ultrasonography use, velocity is measured and used to infer flow. The MCA was chosen because it perfuses approximately 80% of the cerebral hemisphere and can be measured easily and reproducibly. Although phenylephrine was given to maintain MAP within normal limits, this should not have altered our findings as it has been shown not to affect the diameter of the MCA.\(^14\) Constant vessel diameter is suggested further by the unchanged A–V \( D\text{O}_2 \) during the three periods of EEG suppression.

We measured CBF velocity rather than CBF. However, a good correlation between relative changes in flow velocity and CBF has been demonstrated previously.\(^15\)\(^16\) During cerebral venous blood sampling, although there is interpatient anatomical variability in cerebral venous drainage, the right internal jugular vein is recommended for this purpose.\(^17\) Jugular venous bulb sampling and oximetry reflect overall adequacy of global oxygen delivery and consumption.\(^18\)

Brain protection and resuscitation are complex and difficult. The most important strategy is to maintain normoxia and adequate cerebral perfusion pressure, and there is new evidence that mild hypothermia may be of benefit.\(^19\) Timely surgical intervention and other methods to reduce increasing intracranial pressure such as mannitol may also be required. The use of non-steroidal anti-inflammatory agents, ion channel blockers, excitatory amino acid antagonists, free radical scavengers, and cell adhesion molecule and prostaglandin inhibitors have yet to be proved useful.\(^3\)

Suppression of metabolism by anaesthetic agents may also provide significant cerebral protection in focal ischaemia. Anaesthetic agents administered to the point of EEG isoelectricity appear to suppress the brain’s utilization of oxygen that supports electrophysiological activity while leaving cellular integrity unaffected.\(^20\) Michenfelder and Theye\(^21\) showed that high energy phosphate concentrations were better preserved in dogs treated with high-dose thiopental only when there was some electrical activity left and not complete EEG silence after brain damage. This may help explain why anaesthetic agents are ineffective in global ischaemia, when no electrical activity is present.

Although metabolic suppression may play only a small role in the overall scheme of neurological protection,\(^20\) it is often used clinically for cerebral protection and for reducing intracranial pressure.\(^22\) Some evidence does not support a reduction in metabolism as the primary mechanism by which volatile anaesthetic agents may reduce focal ischaemic brain damage.\(^23\)–\(^27\) In addition, Warner and colleagues have shown that EEG burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal ischaemia,\(^28\) but they did not quantify the degree of burst suppression.

If electrical activity is increased in a vulnerable area, suppression allows all available energy to be used for basal requirements. Basal metabolic pathways continue despite EEG suppression as long as oxygen and substrate are supplied. Electrical activity, such as with bursts of activity, increases metabolism. Abolishing this (i.e. complete EEG isoelectricity) should result in only maintenance of basal metabolism.

In dogs, maximal reduction in metabolism was achieved simultaneously with the onset of an EEG pattern of burst suppression–electrical quiescence.\(^5\) Warner and colleagues\(^28\) showed that with thiopental, which is a potent inhibitor of metabolism, there appeared to be no added benefit in using increased doses of the drug with respect to infarct volume size in rats. However, they used doses only for burst suppression and not complete silence. Most studies appear to assume that burst suppression and complete EEG silence are the same. Current human studies have used burst suppression as an end-point for maximal cerebral metabolic suppression.\(^29\)–\(^33\) We intended to highlight the concept that burst suppression is not a single condition but a spectrum, with 0% suppression at one end and 100% at the other. We could not practically analyse cerebral blood flow over a full range of BSR values. Examining the three states of BSR took on average 2 h for study completion. Therefore, we restricted
the study to the three states of 0%, 50% and 100% BSR, but more detailed studies may be appropriate. It has been suggested previously that maximal reduction in cerebral metabolism is reflected in an isoelectric EEG, although burst suppression is associated with only marginally less CMR depression.30 Human studies31–33 investigated propofol and thiopental with regard to physiological effects and overall outcome rather than quantitative infarct size, and used burst suppression rather than EEG silence as an end-point. These results could have been different if EEG silence had been achieved. Furthermore, these studies used a qualitative and not a quantitative description of burst suppression.

While the aim of our study was not to examine the brain protection effects of burst suppression or complete EEG isoelectricity per se, we have shown that the scientific basis on which brain protection can be inferred from a metabolic point of view would be in keeping with complete EEG silence and not merely qualitative burst suppression. There are no previous human studies comparing the two.

The clinical implications of these results need further evaluation, such as how long-term, high-dose anaesthetic agents may affect other organs. For example, the risk of cardiac strain from catecholamines used to maintain cerebral perfusion pressure would need to be balanced against the possible increased cerebral protection effect.

In summary, we have shown that in humans, there is a greater reduction in cerebral blood flow with a completely isoelectric EEG than with 50% burst suppression. If suppression of metabolic activity has a part in cerebral protection, complete EEG silence may give more protection than 50% burst suppression.

References
1 Menon DK, Summors AC. Neuroprotection (including hypothermia). Curr Opin Anaesthesiol 1998; 11: 485–96
3 Michenfelder JD. The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 1974; 41: 231–6
4 Rampel IJ. A primer for EEG signal processing in anesthesia. Review article. Anesthesiology 1998; 89: 980–1002
6 Rampel IJ, Laster MJ. No correlation between electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. Anesthesiology 1992; 77: 920–5
13 Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane, and desflurane during propofol-induced isoelectric electroencephalogram in humans. Anesthesiology 1995; 83: 980–5
21 Michenfelder JD, Theye RA. Cerebral protection by thiopental during hypoxia. Anesthesiology 1973; 39: 510–17


