Electroencephalography (EEG) and somatosensory evoked potentials (SEP) to prevent cerebral ischaemia in the operating room

L’électroencéphalographie (EEG) et les potentiels évoqués somesthésiques (PES) dans la prévention de l’ischémie cérébrale au bloc opératoire

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Received 8 July 2003; revised and accepted 6 January 2004

KEYWORDS
Review; EEG; SEP; Ischaemia

Abstract We review the principal aspects of EEG and SEP to detect and prevent cerebral ischaemia in the operating room during interventions at risk. EEG and SEP are variables that indirectly reflect cerebral blood flow (CBF) provided that anaesthetic regimen, body temperature, and arterial blood pressure of the patient are stable. When CBF decreases and reaches the functional threshold, slowing and/or attenuation of EEG occurs while the amplitude and the latency of cortical SEP are, respectively decreased and lengthened. Based on these changes, numerous criteria corresponding to critical thresholds have been defined. A decrease in EEG amplitude greater than 30% or EEG changes lasting more than 30 s have been considered as significant by clinicians. The main criteria resulting from computerized EEG analysis were a reduction in total power and/or in spectral edge frequency. Regarding SEP, a more than 50% decrease in N20 amplitude and/or a more than 1 ms increase in central conduction time were the most frequently used criteria. According to the bulk of literature, it may be concluded that processed EEG analysis is more sensitive than visual EEG analysis to detect cerebral ischaemia, and that SEP are not less sensitive than conventional EEG. Moreover, literature shows that SEP are as specific as computerized EEG analysis to disclose ischaemia during carotid endarterectomy.

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Résumé Cet article fait le point sur l'utilisation de l’EEG et des PES pour détecter et prévenir l’installation d’une ischémie cérébrale au bloc opératoire, au cours des interventions à risque. Le tracé EEG et les PES sont des index indirects de la perfusion cérébrale, à condition que le régime anesthésique, la température et la pression artérielle du patient soient stables. Lorsque le débit sanguin cérébral (DSC) baisse et atteint le seuil fonctionnel, l’encéphalogramme est ralenti et/ou atténué alors que l’amplitude et la latence des ondes corticales des PES sont respectivement diminuée et allongée. A partir de ces modifications, de nombreux critères correspondant à des seuils limites ont été définis dans la littérature. Pour l’EEG analogique, une baisse d’amplitude supérieure à 30% ou des modifications d’une durée supérieure à 30 s ont été considérées comme signifiantes par le clinicien. Les critères issus de la numérisation de l’EEG portaient sur une baisse de la puissance totale et/ou de la Spectral Edge Frequency (SEF). En ce qui concerne les PES, une baisse d’amplitude de l’onde corticale N20 d’au moins 50% et/ou un allongement du temps de conduction central (TCC) d’au moins 1 ms ont été les critères quantitatifs les plus souvent utilisés. Les données de la littérature tendent à montrer que l’EEG quantifié est plus sensible que l’EEG analogique pour la détection d’une ischémie et que les PES ne sont pas moins sensibles que l’EEG analogique. De plus, pour l’endartériectomie de la carotide (EC), les PES sont aussi spécifiques que l’EEG quantifié.

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Introduction

Brain is extremely sensitive to anoxia and destroyed neurons are never replaced. Therefore, there is a need for specific preventing measures, which justifies neuromonitoring in all these intracerebral or vascular operations carrying some risk of brain ischaemia. These operations are actually those which can give rise to a decrease in cerebral perfusion and/or to the release of micro- and or macro-, solid and/or gas embolism: operation performed under extracorporeal circulation (ECC), open-heart surgery, or carotid endarterectomy (CEA). Neuromonitoring is also justified in operations associated with a provoked arrest of brain perfusion: circulatory arrest during aortic arch surgery, test of ventricular fibrillation after installation of a defibrillator, cross-clamping of an intracerebral artery during brain aneurysm surgery.

Under general anaesthesia, neuromonitoring can be performed through the assessment of brain haemodynamics, follow-up of brain tissue oxygenation, or electrophysiology (for a review,[28,33]).

Brain haemodynamics can be assessed by measuring cerebral blood flow (CBF) or blood flow velocity in brain arteries (transcranial Doppler). The only operating room (OR) available CBF measurement method is xenon clearance, which was principally used to determine the CBF threshold associated with brain dysfunction and to validate other monitoring tools. However, this cumbersome and expensive method only provides discontinuous measures of brain perfusion [23]. Transcranial Doppler only provides measurement of blood flow velocity (especially in the middle cerebral artery), and not of CBF. This distinction is essential, as both measurements have been demonstrated not being correlated with each other [1]; these can even vary in opposite directions when starting ECC under hypothermia [79,107]. Moreover, it may be impossible to measure blood flow velocity in the middle cerebral artery in 10-15% of cases [01]. Despite this, transcranial Doppler is the method of choice to detect embolism [54]. During CEA, the assessment of the degree of brain ischaemia after external and common carotid artery cross-clamping has been performed through measurement of intravascular pressure in the internal carotid artery, distally to the cross-clamping site ("stump pressure") ([108] for a review). According to the literature, the acceptable lower limit for stump pressure varies from 25 to 50 mm Hg. However, several studies demonstrated that the electrophysiological methods were more sensitive than stump pressure measurement for the detection of brain oligoemia [7,16,57,63,82,93].

The pertinence of brain oxygenation follow-up through near infrared spectroscopy (NIRS) was recently evaluated [58,66,92]. One limit of this method is that it also includes measurement of oxygenation of extracerebral tissues (scalp, skull) that depends on the external carotid artery. Indeed, probes are installed on the forehead skin, so that, ideally, a simultaneous measurement of cutaneous blood flow should be performed [37,64]. Moreover, most studies using this technique actually measured frontal lobe, and not whole-brain oxygenation [22].
Brain function can be directly evaluated through EEG and somatosensory evoked potentials (SEP). As reliable SEP can be obtained in about 1 min, both methods can be considered as providing continuous assessment. Moreover, these allow simultaneous assessment of several cortical areas, or even subcortical centers through SEP recording. Finally, EEG and SEP are technically easily applicable in the OR. These advantages are likely to explain why they were widely used to detect brain hypoperfusion.

This article has two main purposes. The first is to review EEG and SEP methods used to detect acute cerebral ischaemia in the operating room. As clinicians must decide whether to use EEG or SEP test, the second purpose is to attempt a comparison between the accuracy of the two methods.

Pathophysiology

A progressive decrease in brain perfusion is first associated with alterations in synaptic transmission and, thereafter, with neuronal destruction. The CBF threshold for both phenomena depends on the method of CBF measurement, species, brain ischaemia model, the type of anaesthesia, and the body temperature. Therefore, the thresholds are extremely variable. However, they can be graphically outlined as a function of the CBF decrease duration (Fig. 1).

**Functional CBF threshold**

**Definition**

Mean normal CBF value is approximately 50 ml/100 g/min. Mild hypoperfusion from the normal range to 22 ml/100 g/min is well tolerated and does not induce neuronal dysfunction. When flow decreases below the functional threshold, EEG and SEP alterations appear. As opposed to the lesion CBF threshold (see below), the functional threshold does not depend on time [4,8].

**Functional CBF threshold values**

A decrease in EEG amplitude and/or an EEG slowing become manifest when mean CBF falls below 22 ml/100 g/min [34,73,95,99,103]. Regarding SEP, studies performed in the anaesthetized baboon have shown that SEP amplitude decreases for CBF values ranging from 16 to 20 ml/100 g/min [5,15]. In humans, 50% reduction in SEP amplitude is observed when flow decreases below 14 ml/100 g/min [70]. Similarly, an increase in the central conduction time (CCT) occurs for CBF values lower than 15 ml/100 g/min [46].

A further decrease in perfusion (7–15 ml/100 g/min) leads to the flattening of the EEG activity [13]. The CBF values resulting in a loss of spontaneous neuronal activities are extremely variable (6–22 ml/100 g/min). This large variability can be
explained by the differences of individual neurons in energy metabolism and local features of irrigation [51]. Cortical SEP disappear for CBF values between 12 and 15 ml/100 g/min [5,15]. Some authors consider that cortical SEP are lost for flow values 20% lower than those giving rise to an isoelectric EEG [81,85].

Physiological meaning of the functional CBF threshold
Some studies have been focused on the changes in brain metabolism induced by a CBF decrease. They have shown that EEG depends on both the intracellular pH (pHi) and the phosphocreatin (PCr) brain concentration [21]. More precisely, a pHi reduction related to anaerobic glycolysis is associated with an EEG flattening, and EEG disappears when the PCr concentration decreases. EEG alterations become manifest before any drop in ATP brain concentration [77]. These results lead some authors to hypothesize that the cessation of spontaneous brain electrical activity was actually an adaptation process by which the metabolism of oxygen-deprived neurons decreases in order to maintain tissue partial oxygen pressure [78]. Because there is no brain infarction at the functional CBF threshold, it is preferable to term this stage "oligaemia" rather than "ischaemia" [9].

In summary, these results demonstrate that a progressive CBF decrease is associated with EEG and SEP alterations, which justifies their usefulness as indirect tools for CBF measurement.

Lesion CBF threshold

Definition
A more severe CBF decrease is associated with a decrease in ATP concentration so that the electrochemical gradient across the neuronal membrane can no more be maintained (anoxic depolarization). Excitatory amino acids are released in the extracellular space. This phenomenon provokes an increase in intracellular Ca, and the production of free radicals (excitotoxicity). The lesion CBF threshold is associated with irreversible neuronal lesions.

Lesion CBF thresholds values
As opposed to the functional threshold, the threshold of CBF below which the tissue becomes irreversibly damaged will progress to infarction depends on the duration of ischaemia, and is around 10 ml/100 g/min for 1-2 h and around 18 ml/100 g/min for permanent ischaemia in the monkey [10,51].

Studies performed with animal models demonstrated a greater susceptibility for infarction of the grey matter than the white matter because the metabolic needs of the neuronal bodies are higher than those of the axons. Moreover, the hippocampus, cortex and basal ganglia are the most vulnerable cerebral structures [50,83].

The ischaemic penumbra zone [6]

Results gained from animal experiments lead to the notion of "ischaemic penumbra", which corresponds to cerebral tissue in which flow is lying between the functional and the lesion threshold. PET-scan studies demonstrated the existence of ischaemic penumbra in patients presenting with transient ischaemic attacks [9,50]. With PET, the penumbra is characterized by a reduced CBF ("misery perfusion"), an increased oxygen extraction fraction, and a relatively preserved oxygen consumption. This has been demonstrated for the first time in humans by Baron et al. [10]. Ischaemic penumbra can evolve in two ways: either brain tissue fully recovers if CBF is rapidly restored or there is an evolution toward necrosis if ischaemia persists or if metabolic needs exceed energy supply.

Overall, a decrease in EEG or SEP amplitude, an EEG slowing or an increase in SEP latency indicate that the functional CBF threshold is reached. These alterations are highly relevant in terms of patient follow-up because they constitute a warning signal, which appears before the appearance of irreversible brain lesions. The lesion CBF threshold will never be reached if adequate measures are taken to increase the CBF (ECC flow increase, blood pressure increase, shunt installation in CEA) or to decrease brain metabolism (increased level of anaesthesia, deeper hypothermia).

Practically, EEG and SEP as monitoring tools present different advantages and drawbacks. Although several EEG and SEP criteria were proposed in the literature to evaluate the critical CBF threshold, their respective sensitivities and specificities are highly variable among studies.

EEG and SEP alterations induced by a decrease in CBF

EEG alterations

Analog EEG

Description of alterations
It is widely admitted that a progressive CBF decrease gives rise to EEG attenuation (i.e. decrease
in amplitude) and slowing (decrease in $\alpha$ (8-13 Hz) and $\beta$ (≥14 Hz) frequencies, increase in $\theta$ (5-7 Hz) and $\delta$ (0.5-4 Hz)) frequencies ([80] for a review).

Some authors refined these observations and proposed a classification of EEG alterations as a function of the degree of hypoperfusion. Thus, a decrease in fast activities is associated with a moderate CBF decrease. It is followed by changes (increase or decrease) in EEG amplitude, simultaneously with appearance of delta rhythms. A severe hypoperfusion is characterized for some authors by a disappearance of $\alpha$ and $\beta$ and a predominance of $\delta$ frequencies [55,111], and for other authors by an at least 75% attenuation of all activities and/or a more than 100% increase of $\delta$ activities slower than 1 Hz [17].

EEG signs of brain oligoemia are more frequently observed in patients with an abnormal preoperative EEG [99]. The type of alterations could also depend on the type of operation. According to Prior [84], the amplitudes of the $\alpha$ and $\beta$ frequency bands are the most relevant follow-up criteria for hypoperfusion induced by a drop in blood pressure during ECC. In this case, an initial amplitude increase is followed by an amplitude decrease in the absence of blood pressure restoration. More specific alterations, i.e. an isolated disappearance of $\delta$ activities and an increase in $\theta$ rhythms amplitude, without any attenuation, were described after cardiac fibrillation [20].

Localization
The above-mentioned alterations can be focal after cross-clamping of a cerebral artery. After cross-clamping of a carotid artery, they are usually ipsilateral but can also be contralateral, or even bilateral in the absence of sufficient collateral circulation, particularly in case of a contralateral carotid occlusion.

Some authors recommend to explore these brain areas that are the most vulnerable to ischaemia, i.e. at the boundary between the anterior and middle cerebral artery territories (paramedian frontal cortex) or between the carotid artery and the basilar trunk (parieto-occipital cortex) [41].

Delay of appearance
EEG changes can be observed within a delay of about 10 s after cardiac fibrillation [25] and 20 s-3 min after carotid artery cross-clamping [8,72].

Criteria for severe hypoperfusion
Studies of analogue EEG gave rise to a lot of quantitative threshold criteria. Despite this bulk of literature, one may consider as clinically significant a more than 30% amplitude decrease and a change of more than 30 s duration.

Digital EEG
The advantage of digital EEG is to provide more condensed data whose interpretation seems more readily accessible. Numerous studies used digital EEG to identify the risk of cerebral ischaemia.

Time and frequency analyses
For the assessment of brain hypoperfusion, spectral EEG analysis through the Fast Fourier Transform (FFT) proved superior to aperiodic analysis, Hjorth’s descriptors, and zero crossing methods [102]. Most criteria of the literature were obtained from spectral analyses.

Data obtained with the FFT were presented either under the form of “compressed spectral arrays” (CSA) or “density modulated spectral arrays” (DSA) [43]. The former type of analysis consists in determining the power-frequency curve for a given time period and to present successive time periods in a same display, with the risk of masking some curve segments by these corresponding to preceding time periods. This drawback is avoided in the DSA, in which power is coded in grey levels. Both CSA and DSA are graphical representations whose principles of visual interpretation are similar to those used in analogue EEG: identification of an overall power decrease (attenuation) and/or a power increase of $\theta$ and $\delta$ frequency bands (slowing) [18,35,45].

Some quantitative frequency and power variables were extracted from the spectra to detect cerebral oligoemia. Among frequency variables, the firstly used criterion was the “spectral edge frequency” (SEF), which was initially defined as the highest frequency that could visually be identified on the CSA or DSA [87,88]. Currently, most studies rely on the SEF 95 [9,72] or the “median frequency power” (MFP) [11], which correspond to the frequency under which 95% and 50% of the global power is contained, respectively. The SEF 95 variability would be less dependent on anaesthesia and less sensitive to artifacts [74]. Other variables were considered: the mean frequency $f_m$ ($f_m = \Sigma (P_i f_i)/\Sigma (P_i)$ where $P_i$ and $f_i$, respectively, correspond to the power and frequency of each frequency band) [102] and the “main dominant frequency” (MDF: mean frequency in the 8-15 Hz frequency band); their high variability makes these techniques unreliable to diagnose cerebral oligoemia [74]. The quantitative criteria that were defined in the literature to predict post-operative ischaemic lesions were mainly based on the SEF. The mostly studied power criteria were the total power, the absolute or rela-
tive band power (for a given frequency band, the ratio between the absolute power of this band and the total power). Computation of relative powers decreases the inter-individual EEG power variability [91]. The most relevant signs of a CBF decrease are a decrease in total power, a decrease in relative $\alpha$ and $\beta$ band powers associated with an increase in the $\delta$ band powers [104]. In simpler terms, a power decrease of the $\alpha$ or the $\alpha$ and $\beta$ band(s) associated with a power increase of the $\delta$ band would be sufficient to diagnose brain hypoperfusion [91,105]. Some indices were also derived from a combination of these variables. For example, brain hypoperfusion can be suspected in the presence of a decrease in the $\alpha/\delta$ power ratio [19] or, conversely, of an increase in the ($\theta + \delta$) ($\alpha + \beta$) power ratio [11]. However, quantitative threshold values for a significant CBF decrease are rarely reported in the literature. A recent approach consisted in considering the $\alpha$ and $\beta$ band power variability rather than the power values of these bands [74]. It was notable that a decrease in the long-term variability of the $\alpha$ power was also described in vascular spasms occurring as a complication of sub-arachnoid haemorrhages [104]. Laterality [91] and symmetry [74] criteria were also derived from power values in order to detect inter-hemispheric perfusion differences.

Topographical analyses
One study evaluated the pertinence of EEG mapping to detect brain oligaemia during ECC [29]. The spatial extent of an amplitude asymmetry or amplitude increase in a new frequency band when compared to the baseline map obtained before cross-clamping was considered as significant for cerebral oligaemia.

SEPs alterations

Why somatosensory evoked potentials?
Somatosensory EPs were much more frequently used than auditory EPs (AEP) or visual EPs (VEPs) for the detection of brain ischaemia because the somatosensory cortical projections are situated on the hemispheric convexity and are, therefore, more readily accessible to scalp electrodes than auditory and visual primary cortical areas [27]. Moreover, SEP are less sensitive to anaesthesia than VEP [61]. Finally, the primary visual projection areas do not belong to the carotid artery territory so that VEPs are without interest in CEA monitoring.

Which SEP?
The choice of a SEP technique depends on which nervous structures are the most at risk in the monitored procedure. The cortical generators of the N20 and N30 to median nerve stimulation are situated in the middle cerebral artery territory and in the middle/anterior cerebral artery boundary zone, respectively. The generators of median nerve SEP obtained in the 200 ms latency range would be situated at the parieto-occipital junction, that is, at the boundary zone between the carotid and basilar trunk perfusion territories [41]. Although lower-limb SEP correspond to a more restricted area of the parietal cortex than median nerve SEP [81], they present the advantage of recruiting a cortical area that belongs to the anterior cerebral artery territory [41,70].

**SEPs alterations induced by brain hypoperfusion**

**Features**
Some authors compared intra-operative SEP to these obtained in awake patients [48,71]. Now, lipophilic anaesthetic drugs can modify sub-cortical conductions, directly influence cortical generators, or decrease the signal-to-noise ratio [40]. Therefore, the baseline SEP must be these obtained before the hazardous manoeuvres, under a stable anaesthetic regimen and with a constant blood pressure.

At the functional CBF threshold, a further CBF decrease gives rise to a desynchronization of cortical neurones and/or a decrease in the number of functional neurones. This provokes an amplitude decrease or even the disappearance of some peaks. Numerous studies proposed to use the amplitude of the parietal N20 as the diagnostic criterion of cerebral oligaemia [23,24,48,52,56,71,75,82,90,94,101]. Now, the most sensitive cortical areas are these situated at the boundary zones between perfusion areas, like the prerolandic area, which is situated at the boundary between the middle and anterior cerebral artery territory. Its function can be evaluated through the frontal N30 whose generator is likely to be close to the supplementary motor area [27,41]. The frontal N30 is particularly interesting because it may be the only altered SEP component in case of a brain hypoperfusion of systemic origin [109].

It is often considered that SEP latencies are less sensitive than amplitudes to a CBF decrease because the metabolic needs of axons (white matter) are lower than those of neuronal bodies (grey matter) [83]. However, the CCT is often measured. This variable actually reflects a heterogeneous conduction corresponding both to the spinal cord, brainstem and hemispheric sub-cortical impulses. Hence, sub-cortical structures are more resistant to brain ischaemia, owing to lower metabolic needs [14].
Affected hemispheres
In CEA, several authors only recorded SEPs generated in the cerebral cortex ipsilateral to the operated carotid (i.e. they stimulated the contralateral median nerve) [48–50,56,69,82,90,94,110]. Hence, SEP alterations can be limited to the contralateral hemisphere, especially in case of a contralateral carotid occlusion [109]. Therefore, as it is the case with the EEG, both hemispheres must be simultaneously monitored.

Criteria
Most studies propose quantitative criteria based on an N20 amplitude decrease and/or a CCT increase. Significant values are a more than 50% decrease in N20 amplitude [23,24,49,52] and a CCT increase of more than 1 ms [42,65] or more than 20% with respect to normal values [101] (normal reference: 6.9 ± 0.6 ms [39]). For some authors, only the association between an at least 50% decrease in N20 amplitude and a 1 ms [32], or even 1.5 ms [69] CCT increase would actually be predictive of brain ischaemia. An original approach is that of Fava et al. [31] who designed a non-dimensional index (NSI: need for shunt insertion) according to the following formula:

$$\text{NSI} = \left( \frac{P25 \text{ latency after carotid cross-clamping}}{P25 \text{ latency before carotid cross-clamping}} \right) - \left( \frac{N20-P25 \text{ peak-to-peak amplitude after carotid cross-clamping}}{N20-P25 \text{ peak-to-peak amplitude before carotid cross-clamping}} \right)$$

According to these authors, a shunt is needed for NSI values higher than 0.5. However, the NSI has never been intra-operatively validated.

Guérit et al. [42] proposed qualitative criteria. These authors subdivided SEP alterations into three types, as a function of the severity of brain hypoperfusion during CEA. The more important the CBF decrease, the earlier the affected SEP components. Thus, minor alterations correspond to parietal P45 and/or frontal N30 desynchronization. Moderate alterations are characterized by P27 changes, in addition to a desynchronization or a disappearance of P45 and N30. Severe alterations correspond to the disappearance of all parietal components occurring after N20 and of frontal components, usually associated with a more than 1 ms CCT increase, or to the disappearance of all cortical, parietal and frontal, components. Shunt installation is decided on the basis of the severity of abnormalities, the delay with respect to carotid cross-clamping, their duration and their possible association with a drop in blood pressure. The main relevance of these qualitative criteria is that they also take into account the frontal N30 and the parietal P27 and P45, which are more sensitive to brain ischaemia than the parietal N20 and the CCT [41].

Thus it appears that, while the SEP alterations following a critical CBF decrease were clearly defined qualitatively, the definition of unequivocal quantitative criteria for an acceptable CBF decrease is still matter of debate. As shown in the next paragraph, numerous criteria have been considered in the literature and they are hardly comparable with each other.

Respective advantages and drawbacks of EEG and SEPs

Advantages that are common to both methods
Both direct CBF studies and measurements of blood flow velocity in cerebral arteries only provide data on brain perfusion. On the contrary, EEG and SEP directly assess the function of brain tissue, which depends on both energy supply (CBF) and needs (metabolism).

EEG and SEP are non-invasive and easily implemented in the OR. Unlike direct CBF measurement by clearance methods, they provide nearly continuous measurement of brain function.

Finally, both methods are inexpensive [104].

Limits that are common to both methods

Methodological limits
As opposed to transcranial Doppler, EEG and SEP have no aetiological specificity, i.e. they do not allow differentiating a CBF decrease due to haemodynamic disturbances or embolism.

Dependence on anaesthesia and body temperature
Both anaesthesia and hypothermia (which can be induced to further decrease brain metabolism during provoked circulatory arrest or ECC) influence brain function. Both induce progressive, bilateral, and symmetrical EEG and SEP alterations (for a review: [41,96]).

Except ketamine, most anaesthetic drugs induce similar EEG and cortical SEP changes. Most anaesthetic drugs first give rise to an EEG fastening consisting of the disappearance of α rhythms and appearance of β rhythms, followed by a progressive EEG synchronization and slowing (appearance of θ and δ rhythms). A deeper level of anaesthesia is associated with the burst-suppressive pattern, followed by a progressive electrocerebral silence. The effects on cortical SEPs are more marked than these on sub-cortical and peripheral components.
and consist of a latency increase and amplitude decrease. Ketamine is different in that the disappearance of the α rhythms is immediately followed by the appearance of a rhythmic β activity preceding the occurrence of δ waves. Moreover, ketamine, like etomidate, gives rise to an increase in SEP amplitude. High dosages of opiate drugs, commonly used in heart surgery, may be associated with EEG slowing with high-amplitude δ waves, but have little influence on SEP (at least for components earlier than 100 ms). Finally, curarization does not influence electrophysiological measurements (with the possible exception of an increase in SEP amplitude due to a better signal-to-noise ratio consequent to removal of muscle artifacts).

Moderate hypothermia (body temperature higher than 30 °C) is associated with a decrease in amplitude and slowing of the EEG. The effect of body temperature on quantitative EEG is still matter of controversy: while Levy [67,68] did not demonstrate any relationship between cooling down and SEP, Russ et al. [89] found SEF to be linearly correlated with tympanic temperature. In SEP, all peaks remain identifiable, but with higher latencies. For body temperatures lower than 30 °C, later SEP components first disappear, followed by earlier components. The EEG becomes isoelectric at 22–25 °C. In SEP, N20 and P14 disappear at 15–26 °C and 12-20 °C (nasopharyngeal temperatures), respectively, [38,59]. These studies demonstrate that the intra-operative detection of brain dysfunction requires stable anaesthetic levels and body temperature after baseline determination.

Interpretation
The EEG and SEP interpretation must be performed by skilled specialists, and there exists some part of subjectivity, especially in EEG interpretation. This bias may be reduced by EEG digitalization, which can give rise to a more comprehensive and less subjective study. On the contrary, quantified EEG can produce a wide set of data from which the more relevant parameters should be cautiously extracted. There are currently no unanimously accepted criteria for critical brain hypoperfusion. Several authors consider that the diagnosis of brain ischaemia may not rely on an isolated, EEG or SEP, criterion [67,111].

Sensitivity and specificity
Definitions [47,53]
Clinicians must decide whether to use EEG or SEP test in a patient at risk. A crucial step in the evaluation of the two tests is the assessment of diagnostic accuracy, i.e. the ability of the test to determine correctly the presence or the absence of cerebral ischaemia. The two most commonly reported measures to estimate test accuracy are sensitivity and specificity. Sensitivity is the probability that a test result is positive in patients with cerebral ischaemia while specificity is the probability that the test result is negative in patients without cerebral ischaemia [53].

<table>
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<th>Table 1</th>
<th>EEG or SEP test accuracy.</th>
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<tr>
<td>Cerebral ischaemia</td>
<td>Yes</td>
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<tr>
<td>Test Tested positive</td>
<td>A</td>
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<tr>
<td>(EEG or SEPs) Tested negative</td>
<td>C</td>
</tr>
<tr>
<td>A, B, C, and D are the number of observed patients in each cell. A are the true positive; B are the false positive; C are the false negative; D are the true negative. Sensitivity = true positive rate = A / (A + C). Specificity = true negative rate = D / (D + C).</td>
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Main sources of bias in the calculation of accuracy
Practically, it is extremely difficult, if not impossible, to precisely calculate these parameters. There is no golden standard test to which the two monitoring techniques could be compared. Thus the only basis for comparison is the presence or the absence of the disease of interest, i.e. cerebral ischaemia.

First, to determine accuracy, it must be proven that an ischaemic event had occurred during the monitoring period. That means that the new post-operative deficit is actually consecutive to an intra-operative reduction in perfusion. Hence, it is known that ischaemia can also occur during the post-operative period (brain haemorrhage induced by reperfusion hyperaemia, thrombosis) [98]. If one takes into account post-operative strokes not related to intra-operative cerebral ischaemia for the determination of accuracy, the number of false negative will increase and consequently the sensitivity will decrease. For instance, in all patients of our 1997 series [42] disclosed neurological sequelae despite unchanged SEP during the CEA procedure itself, either there was delayed embolism or
the procedure was immediately followed by coronary bypass; conversely, a transient ischemic attack was observed in only one out of 152 patients undergoing isolated CEA who were not shunted, based on the absence of intra-operative SEP changes.

The second main issue is that neurophysiological monitoring during carotid and cardiac surgery very often gives rise to an interactive strategy like the insertion of a shunt in CEA and/or the elevation of arterial blood pressure by means of drugs. Such strategies aim to increase cerebral perfusion, and consequently reverse the observed neurophysiological alterations. In this case, the number of true positive is decreased while the number of true negative is increased. As a result, sensitivity is lowered and specificity is raised. In the extreme, sensitivity cannot be calculated because there is no case of cerebral ischaemia.

Comparison between both methods

Recordings
SEP recording requires a lower number of electrodes than EEG recording and provides less data. However, SEP provide less widespread cortical assessment when compared to multichannel EEG. For example, median nerve SEP do not evaluate the anterior cerebral artery territory. Conversely, SEP provide brain-stem and sub-cortical assessment while EEG does not.

Because of averaging, SEP are less sensitive than the EEG to the environmental electrical noise in the OR [38]. By contrast, their recording requires more time than the EEG, owing to the time required by the averaging process (1-2 min) [33,83].

Because they disappear at lower body temperatures and for deeper anaesthetic levels than the EEG, SEP are less influenced by these factors [41,70].

EEG is modified by craniotomy and is, therefore, of limited interest during surgery of intracerebral aneurysms [70].

Accuracy
We performed a systematic review of primary studies to evaluate the accuracy of EEG and SEP tests. Studies were included if they comply with the following requests. The studies had to be referenced in the PUBMED database and had to be published in English language. EEG or SEP criteria indicative of cerebral oligaemia had to be clearly defined. The results section had to allow the determination of each cell of Table 1. We considered that patients had suffered from cerebral ischaemia when they awoke from anaesthesia with a new post-operative neurologic deficit. The deficit could be reversible or permanent. When EEG or SEP criteria reversed during the operation and the patient did not have a new deficit, the patient was considered as a true negative.

We first performed calculations of sensitivity and specificity of each primary study. Provided that they are several thresholds for a given test and that the thresholds of a given test could vary with the prevalence of the disease, we also calculate sensitivity and specificity of pooled data (53).

Studies applying both monitoring techniques in the same patients
The comparison of the accuracy of two diagnostic tests should ideally be based on studies in which the two tests are applied to each patient [53]. Six studies fulfilled this requirement (Table 2). Sensitivity and specificity were calculated as defined in Table 1.

The mean SEP sensitivity (0.57) appears higher than that of EEG (0.20) while mean EEG and SEP specificities are similar (respectively, 0.92 and 0.92). When the data are pooled, SEP tests are found more sensitive and specific (respectively, 0.60 and 0.97) than EEG monitoring (respectively, 0.20 and 0.95). Odds ratios of SEP and EEG are, respectively, 48.26 and 4.98 suggesting the superiority of SEP tests.

Studies applying either EEG or SEP monitoring technique
Obtaining diagnostic accuracy information for the two tests from different primary studies is a weaker design but there is a wealth of studies using one of the two tests. Only these studies dealing with a sufficient number of patients (>99) were considered. Sensitivity and specificity were calculated as defined in Table 1.

EEG sensitivity and specificity
The study design, the threshold, and the accuracy of the relevant literature having used analog EEG are given in Tables 3 and 4. The mean values of sensitivity and specificity are 0.46 and 0.89, respectively. The sensitivity of analog EEG is quite smaller (0.27) when one pools the data of the nine studies while specificity (0.87) is close to mean specificity. Odds ratio of analog EEG is 2.52.

The same results estimated from digital EEG are given in Tables 5 and 6 with mean sensitivity and specificity of 0.55 and 1.00, respectively. After pooling the five studies, the accuracy of quantified EEG is characterized by a sensitivity of 0.58, a specificity of 0.99, and an odd ratio of 878.63. Thus it appears, whether considering separate or pooled data, that the criteria issued from EEG quantifica-
Table 2  EEG and SEP accuracy in studies in which both techniques were used in the same patients.

<table>
<thead>
<tr>
<th>References</th>
<th>Interventions</th>
<th>Methodologies</th>
<th>Thresholds for classifying the test as positive</th>
<th>Test</th>
<th>New post-operative deficit</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pozzessere et al. [82]</td>
<td>CEA with SS</td>
<td>Eight EEG channels (needle electrodes)</td>
<td>Lateralized or generalized slowing</td>
<td>+</td>
<td>0</td>
<td>6</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analog EEG</td>
<td>Or lateralized or generalized slow waves. Or</td>
<td>-</td>
<td>2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td>loss of fast activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lam et al. [65]</td>
<td>CEA without shunting</td>
<td>16 EEG channels</td>
<td>Analog EEG</td>
<td>+</td>
<td>1</td>
<td>5</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td>More than 50% increase of δ activities and/or</td>
<td>-</td>
<td>1</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 50% decrease of N20 amplitude</td>
<td>more than 50% decrease of α and β</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fava et al. [31]</td>
<td>CEA with SS</td>
<td>Eight bipolar derivations</td>
<td>Loss of fast frequencies</td>
<td>+</td>
<td>0</td>
<td>15</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analog EEG</td>
<td>Or appearance of slow waves Or amplitude</td>
<td>-</td>
<td>3</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td>reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearse et al. [56]</td>
<td>CEA with SS</td>
<td>16 bipolar EEG channels</td>
<td>Decrease of fast activities (α and β), increase of δ activities, amplitude variations</td>
<td>+</td>
<td>0</td>
<td>1</td>
<td>Undetermined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analog EEG</td>
<td></td>
<td>-</td>
<td>0</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td>More than 50% amplitude decrease of N20</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Fiori and Parenti [32]</td>
<td>CEA with SS</td>
<td>Two bipolar channels (right and left central-parietal)</td>
<td>Ipsilateral graphical SEF &lt;7 Hz</td>
<td>+</td>
<td>1</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantified EEG: FFT, frequency band: 1-30 Hz, epoch duration: 2 s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td></td>
<td>-</td>
<td>1</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>Lacroix et al. [62]</td>
<td>CEA with SS</td>
<td>Four bipolar EEG channels (needle electrodes)</td>
<td>More than 50% decrease of N20 amplitude</td>
<td>+</td>
<td>1</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantified EEG</td>
<td>Or more than 1 ms CCT increase</td>
<td>-</td>
<td>1</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median nerve SEP</td>
<td>New asymmetry of more than 30% of the total</td>
<td>+</td>
<td>1</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only contralateral median nerve stimulated</td>
<td>spectral power with loss of the high frequencies ipsilateral to the clamp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SEP</td>
<td>Reduction of the N20-P25 amplitude of more</td>
<td>+</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EEG</td>
<td>than 50%</td>
<td>-</td>
<td>1</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pooling data</td>
<td>And/or an increase in the latency of N20 of</td>
<td>+</td>
<td>2</td>
<td>28</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SEP</td>
<td>more than 1 ms</td>
<td>-</td>
<td>8</td>
<td>558</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pooling data</td>
<td></td>
<td>+</td>
<td>6</td>
<td>17</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Table 3  Analog EEG changes indicative of cerebral oligaemia (SS = selective shunting).

<table>
<thead>
<tr>
<th>References</th>
<th>Interventions</th>
<th>EEG methodologies</th>
<th>Thresholds for classifying the test as positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al. [7]</td>
<td>CEA with SS</td>
<td>Needle electrodes</td>
<td>Generalized bilateral slowing Or lateralized slow activity Or generalized slowing with lateralized suppression of slow activity Or generalized suppression of fast frequencies without slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eight bipolar derivations</td>
<td></td>
</tr>
<tr>
<td>Chiappa et al. [18]</td>
<td>CEA with SS</td>
<td>Nine surface electrodes</td>
<td>More than 50% ipsilateral or bilateral attenuation And/or slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eight bipolar derivations</td>
<td></td>
</tr>
<tr>
<td>Green et al. [36]</td>
<td>CEA with SS</td>
<td>Unknown</td>
<td>Amplitude decrease within 3 min after cross-clamping Or loss of activity within 3 min after cross-clamping Persisting attenuation of α and β activities Or increase of δ rhythm</td>
</tr>
<tr>
<td>Kresowik et al. [60]</td>
<td>CEA with SS</td>
<td>16 EEG channels</td>
<td></td>
</tr>
<tr>
<td>Facco et al. [30]</td>
<td>CEA with SS</td>
<td>Needle electrodes</td>
<td>More than 50% decrease of fast activities Or presence of δ activities Or signal flattening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-16 electrodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar derivations</td>
<td></td>
</tr>
<tr>
<td>Fava et al. [31]</td>
<td>CEA with SS</td>
<td>Eight bipolar derivations</td>
<td>Loss of fast frequencies Or appearance of slow waves Or amplitude reduction</td>
</tr>
<tr>
<td>Stoughton et al. [97]</td>
<td>CEA with SS</td>
<td>Eight electrodes</td>
<td>With respect to the pre-clamping baseline More than 50% amplitude decrease of α and β rhythms Or persistence of δ activity on at least one hemisphere</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EEG montage unknown</td>
<td></td>
</tr>
<tr>
<td>Wellman et al. [106]</td>
<td>CEA with SS</td>
<td>16 bipolar derivations</td>
<td>Loss of fast activities Or slowing of the background rhythm Or suppressive EEG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>General or local anaesthesia</td>
<td></td>
</tr>
<tr>
<td>Deriu et al. [26]</td>
<td>CEA with systematic shunting</td>
<td>Unknown</td>
<td>Focal or diffuse EEG δ waves Or homolateral slowing of the fast waves Or bilateral slowing of the fast waves Or levelling of the rhythms</td>
</tr>
</tbody>
</table>

Table 4  Accuracy of analog EEG (the thresholds used for the tests are those described in Table 4).

<table>
<thead>
<tr>
<th>References</th>
<th>New post-operative deficit</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tests</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Baker et al. [7]</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0</td>
<td>157</td>
</tr>
<tr>
<td>Chiappa et al. [18]</td>
<td>+</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>3</td>
<td>231</td>
</tr>
<tr>
<td>Green et al. [36]</td>
<td>+</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>28</td>
<td>432</td>
</tr>
<tr>
<td>Kresowik et al. [60]</td>
<td>+</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>12</td>
<td>319</td>
</tr>
<tr>
<td>Facco et al. [30]</td>
<td>+</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0</td>
<td>374</td>
</tr>
<tr>
<td>Fava et al. [31]</td>
<td>+</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>3</td>
<td>127</td>
</tr>
<tr>
<td>Stoughton et al. [97]</td>
<td>+</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>Wellman et al. [106]</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0</td>
<td>217</td>
</tr>
<tr>
<td>Deriu et al. [26]</td>
<td>+</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1</td>
<td>293</td>
</tr>
<tr>
<td>Pooled data</td>
<td>+</td>
<td>17</td>
<td>322</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>47</td>
<td>2245</td>
</tr>
</tbody>
</table>
tion are more accurate than those obtained from analog EEG. This result is in keeping with literature [18,19,76,80,81]. Interestingly, some authors consider digital EEG to be less sensitive for less severe CBF decreases [55] or slowly developing brain hypoperfusion [32]. Regarding each individual criterion, two studies concluded on a higher sensitivity of the global EEG power, when compared to the SEF, for the detection of cerebral oligaemia [44,111]. Finally, it would appear that EEG mapping would be less specific as it is associated with a high detection rate of EEG abnormalities that are non-correlated with post-operative clinical changes [2].

**SEP sensitivity and specificity**

The results are summarized in Table 7. It must be underlined that the number of false negative may increase when only the median nerve contralateral to the operated carotid artery is stimulated. The mean values of sensitivity and specificity are 0.51 and 0.98, respectively. The sensitivity and the specificity of pooled data (0.52 and 0.98, respectively) are very close to these values. Odds ratio in the pooled population is of 60.42.

Regarding the selected studies applying either EEG or SEP monitoring technique, we may conclude that median nerve SEP sensitivity is higher than the sensitivity of analog EEG but lower than that of digital EEG test. Furthermore, SEP are more specific than analog EEG and they are quite as specific as digital EEG.

**Conclusions**

Both EEG and SEPs are readily applicable in the OR and provide indirect assessment of brain perfusion. Therefore, monitoring by one of both methods must be considered as mandatory whenever there is some probability of brain ischaemia and some means of early neuroprotection are available.

Ideally, the method must follow-up all these structures that are exposed to ischaemia. Their spatial and temporal resolutions must be as precise
Practically, SEP provide less widespread cortical assessment as the EEG but are less sensitive to the environmental electrical noise. Their recording requires more time, which is not really an impetus for early detection of ischaemia.

The comparison of the accuracy of EEG and SEP tests is delicate. However, we attempted to classify the methods either by considering primary studies separately or by pooling the data. The conclusions drawn are the same. The present meta-analysis suggests that SEP monitoring is (1) as sensitive as analog EEG monitoring and (2) as specific as quantitative EEG monitoring techniques for the early detection of cerebral oligaemia.

Nevertheless, standardization of the tests and of the thresholds is required to allow further meta-analysis or multicentric studies. There is also an urgent need of more studies examining simultaneous EEG and SEP recordings.

References


EeG and SEP to prevent cerebral ischaemia in the operating room

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