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Correlation of Regional Cerebral Blood Flow with Ischemic Electroencephalographic Changes during Sevoflurane–Nitrous Oxide Anesthesia for Carotid Endarterectomy

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Background: **Carotid endarterectomy necessitates temporary unilateral carotid artery occlusion. Critical regional cerebral blood flow (rCBF) has been defined as the rCBF below which electroencephalographic (EEG) changes of ischemia occur. This study determined the $rCBF_{50}$, the rCBF value at which 50% of patients will not demonstrate EEG evidence of cerebral ischemia with carotid cross-clamping.**

Methods: **Fifty-two patients undergoing elective carotid endarterectomy were administered 0.6–1.2% (0.3–0.6 minimum alveolar concentration) sevoflurane in 50% nitrous oxide (N_2O). A 16-channel EEG was used for monitoring. The washout curves from intracarotid ^{133}Xenon injections were used to calculate rCBF before and at the time of carotid occlusion by the half-time ($t_{1/2}$) technique. The quality of the EEG with respect to ischemia detection was assessed by an experienced electroencephalographer.**

Results: **Ischemic EEG changes developed in 5 of 52 patients within 3 min of carotid occlusion at rCBFs of 7, 8, 11, 11, and 13 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. Logistic regression analysis was used to calculate an $rCBF_{50}$ of 11.5 ± 1.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ for sevoflurane. The EEG signal demonstrated the necessary amplitude, frequency, and stability for the accurate detection of cerebral ischemia in all patients within the range of 0.6–1.2% sevoflurane in 50% N_2O.**

Conclusions: **The $rCBF_{50}$ of 0.6–1.2% sevoflurane in 50% N_2O, as determined using logistic regression analysis, is 11.5 ± 1.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. Further, in patients anesthetized in this manner, ischemic EEG changes due to carotid occlusion were accurately and rapidly detected. (Key words: Volatile anesthetics; logistic regression analysis; cerebral ischemia; human subjects.)**

IN patients undergoing carotid endarterectomy with continuous 16-channel electroencephalographic (EEG) monitoring, investigators have measured regional cerebral blood flow (rCBF) before and after occlusion of the carotid artery and correlated EEG changes of ischemia with rCBF.[1-3] Michenfelder *et al.*[4] defined the critical rCBF as the rCBF below which more than 50% of patients developed ipsilateral EEG changes of ischemia within 3 min of carotid occlusion. The critical rCBF varies depending on the volatile anesthetic used. In patients receiving nitrous oxide (N_2O) plus a volatile anesthetic, the critical rCBF is approximately 20, 15, and 10 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ for halothane, enflurane, and isoflurane, respectively.[1-4]

Sevoflurane is a new inhalational anesthetic. Based on its relative insolubility, the rate of clearance[5] and awakening from sevoflurane anesthesia is faster than that from anesthesia with halothane or isoflurane.[6,7] The nonpungent odor of sevoflurane contributes to a smooth awakening with less coughing and bucking.[8]

There are no studies supporting the use of sevoflurane in patients undergoing carotid endarterectomy in which continuous EEG monitoring is used to guide the surgeon in selective carotid shunt placement. In addition, the relation between rCBF and the likelihood that the patient will experience an ischemic EEG change with carotid cross-clamping in sevoflurane-anesthetized patients is unknown. In this study, we determined the EEG pattern associated with 0.4-0.6 minimum alveolar concentration sevoflurane in 50% N_2O and oxygen and the rCBF at which 50% of patients show carotid cross-clamp-related ischemic EEG changes.

Methods

This study was approved by the institutional review board of the Mayo Clinic. Fifty-two patients classified

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as American Society of Anesthesiologists physical status I–III who were aged 45–85 yr and scheduled for elective carotid endarterectomy were enrolled in the study after giving informed consent. Patients experiencing symptomatic congestive heart failure, acute neurologic instability, or baseline EEG asymmetry severe enough to obscure the detection of cerebral ischemia were excluded from participation. Intraoperative monitoring included noninvasive sphygmomanometer, electrocardiogram, pulse oximetry, indwelling radial artery catheter for pressure and blood gas measurements, esophageal stethoscope with temperature probe, peripheral nerve stimulator, mass spectrometry to determine end-tidal carbon dioxide tension (E_tCO_2) and inspired and expired sevoflurane concentrations, and continuous 16-channel EEG. A baseline EEG was obtained before any anesthetic agents were given. The EEG was continuously monitored by an experienced electroencephalographic technician under the direction and review of a neurologist. Anesthesia was induced with 2–7 mg/kg thiopental given intravenously in incremental doses. Laryngoscopy and intubation of the trachea was facilitated with 0.1–0.2 mg/kg vecuronium given intravenously. Narcotics and benzodiazepines were avoided in all patients during surgery. Patients having their preoperative cerebral angiogram on the day of surgery were permitted to receive small doses of fentanyl and midazolam for sedation. The dosages and the time elapsed between their administration and the start of the carotid endarterectomy were recorded. The lungs were mechanically ventilated to maintain a partial pressure of carbon dioxide (Pa_{CO_2}) of 35–45 mmHg as estimated by E_{tCO_2} and confirmed by arterial blood gas analysis. Anesthesia was maintained with 0.6–1.2 vol% sevoflurane (0.3–0.6 minimum alveolar concentration) and 50% N_2O in oxygen. With guidance from the electroencephalographer, the inspired concentration of sevoflurane was adjusted within these limits to obtain the best EEG tracing possible to demonstrate cerebral ischemia. The EEG was judged to be adequate by the electroencephalographer if it possessed sufficient amplitude and high frequency activity necessary for to detect ischemia. Neuromuscular blockade was maintained with vecuronium. The patient's normal preoperative blood pressure was determined by examining all available blood pressure readings within the preceding 24 h and determining their average. Intravenous infusions of phenylephrine, esmolol, and nitroprusside were used to maintain mean arterial pressure within the normal preoperative range. Injection of the carotid body–sinus complex with 1% lidocaine to stabilize hemodynamics was performed at the discretion of and by the neurosurgeon.

An arterial blood gas was drawn within the first 30 min after intubation to verify Pa_{CO_2} of 35–45 mmHg. Regional CBF measurements were obtained before and at the time of carotid occlusion. At the time of each rCBF determination, mean arterial pressure, Pa_{CO_2}, Pa_{O_2}, end-tidal concentration of sevoflurane, hemoglobin concentration, esophageal temperature, and type of vasoactive drug being administered were recorded. A temporary carotid shunt was placed at the discretion of the neurosurgeon based on rCBF and EEG data. Elapsed time between surgical occlusion of the carotid artery and onset of ischemic EEG changes was recorded. In accordance with previous studies, carotid cross-clamp–related ischemic EEG changes were defined as those occurring within 3 min of carotid cross-clamp application.[1,3,4] Ischemic EEG changes were characterized as loss of ipsilateral high-frequency activity and altered amplitude.[4] The effect of shunt placement or postendarterectomy reperfusion on ischemic EEG changes was noted. New postoperative neurologic deficits detected on emergence were documented.

A single extracranial collimated sodium iodide scintillation detector was placed over the posterior parietal boss (in the distribution of the middle cerebral artery), and the rCBF was determined by analysis of the clearance curves of ^{133}Xe (200 μCi) injected through a 27-gauge needle into the internal carotid artery. The preocclusion rCBF value was obtained once the carotid artery was completely exposed surgically and was ready for arteriotomy. A second ^{133}Xe injection was performed and, once ^{133}Xe uptake was detected over the cerebral hemisphere, the common carotid artery was clamped and the washout used to calculate the occlusion rCBF value. Total fresh gas flow through the breathing circuit was 5 l/min to minimize rebreathing of ^{133}Xe.

The clearance curves of ^{133}Xe were used to calculate rCBF by the half-live method as described by Messick *et al.*[3] This method derives an rCBF value that depends largely on gray matter flow. When the ^{133}Xe injection for the occlusion blood flow was done before the preocclusion curve had returned to baseline (a scenario in which the decay of the occlusion curve is altered by the underlying decay of the previous preocclusion ^{133}Xe injection), a logarithmically corrected half-time method was used.[9] Using this correction, the decay of the preocclusion curve can be extrapolated and then subtracted

from the decay of the apparent occlusion curve, thus eliminating the declining baseline and permitting a more accurate measurement of the occlusion curve. This corrected occlusion curve is then analyzed according to the half-life method described before.

Statistical Analysis

The study participants were grouped as those with and those without EEG changes of ischemia. The two groups were compared with regard to rCBF, mean arterial pressure, Pa_{CO_2}, Pa_{O_2}, end-tidal sevoflurane concentration, hemoglobin, and temperature at the time of the preocclusion and occlusion rCBF determinations using Student's unpaired *t* test. Differences were considered significant when probability values were <0.05. Unless stated otherwise, data are reported as means ± SD. The $rCBF_{50}$ or the regional cerebral blood flow at which 50% of sevoflurane- and N_2O-anesthetized patients showed EEG slowing with carotid cross-clamping was determined using logistic regression analysis.[10] The standard deviation in $rCBF_{50}$ was estimated from the standard deviation in the slope and intercept of the logistic regression line.

Logistic regression analysis is used to determine the interaction between a quantal dependent variable (response is either present or absent) and a continuous independent variable and is frequently used to determine dose-effect relations in pharmacology.[10] In this study, the quantal dependent variable is the presence or absence of an EEG change within 3 min of carotid cross-clamping, and the independent continuous variable is rCBF. This analysis permits the use of all occlusion rCBF values, rather than rCBF flow ranges, and is used to calculate the slope and the variance in the slope of the relation between the probability that there will be no EEG change and the rCBF. The $rCBF_x$ and the standard deviation in $rCBF_x$ can then be calculated, where x can vary from 5 to 95 and denotes the percentage of patients that will not experience an EEG change with carotid cross-clamping. This analysis also lends itself to prospective comparisons of $rCBF_x$ as a function of treatment. In the present study, we approximated the definition for critical rCBF defined by Michenfelder *et al.*[4] with the definition $rCBF_{50}$. The 90% confidence interval in the relation between rCBF and the probability of no EEG change was calculated from the variance and covariance in the slope and slope intercept of the logistic regression curve.[10]

Table 1. Patient Demographics

Variable	Value
Sex	
Male	40
Female	12
Age (yr)	68.9 ± 8.5
Height (cm)	170 ± 8.5
Weight (kg)	81 ± 15

Values are mean ± SD.

Results

Table 1 shows the characteristics of the study participants.

Seven patients received fentanyl and midazolam sedation for their preoperative angiograms on the same day as their carotid surgery. The largest dosages administered to a single patient were 100 μg fentanyl and 2 mg midazolam. The shortest time interval between sedative administration and surgery was 4 h.

The EEG pattern consisted of widespread diffuse delta slowing maximum in the frontal polar regions with a rhythmic fast 8-12 Hz component maximum anteriorly and demonstrated only minimal fluctuations with changes in the level of surgical stimulation. Carotid cross-clamp-related ischemic EEG changes were readily observed in patients with and without baseline EEG symmetry using this anesthetic regimen.

Forty-seven patients had unchanged EEG tracings during cross-clamping, whereas five patients had ischemic EEG changes. The occlusion rCBF values in the EEG change group were 7, 8, 11, 11, and 13 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. The group without ischemic EEG changes had two patients with occlusion rCBF ≤13 (8 and 13 $ml \cdot 100\ g^{-1} \cdot min^{-1}$), with the remaining 45 patients having rCBFs >13 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (fig. 1A). The $rCBF_{50}$ was 11.5 ± 1.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ using the logarithmically corrected half-life technique. Figure 1B shows the logistic regression curve and the corresponding 90% confidence interval depicting the relation between rCBF and the probability of no ischemic EEG change with carotid cross-clamping.

At the time of the occlusion rCBF determination, 42 of 47 patients without EEG changes required vasoactive infusions to achieve their target blood pressures (24 phenylephrine, 16 nitroprusside, and 2 required both simultaneously). Four of five in the EEG change group needed vasoactive infusions (two phenylephrine and two nitroprusside).

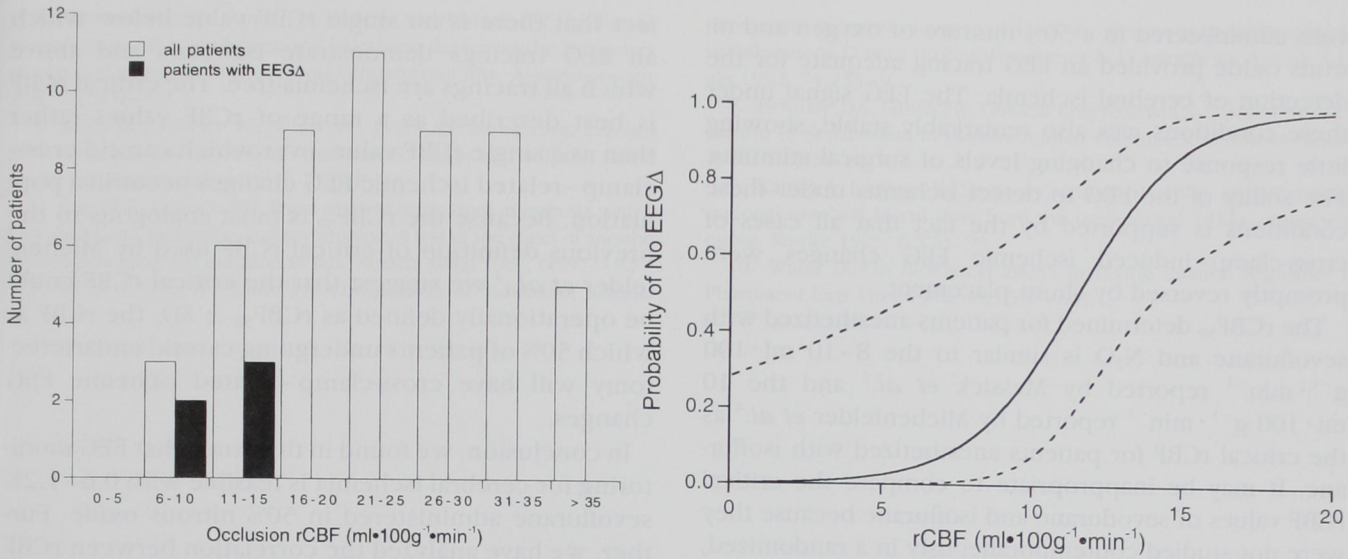

Fig. 1. (*A*) Distribution of regional cerebral blood flow (rCBF) values obtained from all patients (with and without ischemic electroencephalography [EEG] Δ) at the time of carotid occlusion. The occlusion rCBF values of the five patients exhibiting carotid cross-clamp–related ischemic EEG changes are shown separately as black bars. (*B*) The logistic regression curve with 90% confidence interval depicting the relation between rCBF and the probability of no carotid cross-clamp–related EEG change. The logistic regression curve is generated using the equation $P = e^{(\alpha+\beta x)}/(1 + e^{(\alpha+\beta x)})$, where P is the probability of no EEG change, α and β are the intercept and slope estimates from the logistic regression analysis, and x is rCBF.

The two groups were compared with regard to average mean arterial pressure, Pa_{CO_2}, Pa_{O_2}, end-tidal sevoflurane concentration, hemoglobin, and temperature recorded at the time of the preocclusion rCBF and the occlusion rCBF (table 2). There were no differences except for occlusion rCBF.

No new postoperative neurologic deficits were detected in any patient.

Discussion

At this institution, the integrity of cortical function during carotid endarterectomy is monitored using 16-channel EEG. Carotid shunts are selectively placed by the surgeon when the EEG demonstrates evidence of cerebral ischemia after carotid cross-clamp application in a patient with adequate cerebral perfusion pressure. To this end, the ability to accurately assess the EEG for cerebral ischemia is of paramount importance. Any anesthetic agent used under these monitoring conditions must simultaneously provide for adequate anesthesia and an EEG that can demonstrate ischemia. We were careful to exclude patients from the study whose preoperative EEG readings were severely depressed as the result of previous strokes because this made the detection of new intraoperative EEG changes difficult. Patients with mild preoperative EEG abnormalities who exhibited enough fast activity of sufficient amplitude were included in the study at the discretion of the electroencephalographer. In all study patients, an end-tidal sevoflurane concentration within the range of 0.6–1.2

Table 2. Comparison of Mean ± SD Values for rCBF, MAP, Pa_{CO_2}, Pa_{O_2}, E_t Sevoflurane, Hgb, and Esophageal Temperature in Patients with and without Carotid Cross-clamp Related Ischemic EEG

Variable	Time	EEG Δ (n = 5)	No EEG Δ (n = 47)	*P* Value
rCBF (ml · 100 g^{-1} · min^{-1})	pre	37 ± 5	41 ± 13	0.51
	occ	10 ± 2	26 ± 10	0.0004
MAP (mmHg)	pre	112 ± 14	112 ± 15	0.99
	occ	118 ± 17	119 ± 16	0.88
Pa_{CO_2} (mmHg)	pre	40 ± 2	40 ± 3	0.92
	occ	41 ± 1	41 ± 2	0.85
Pa_{O_2} (mmHg)	pre	150 ± 46	169 ± 41	0.35
	occ	161 ± 39	170 ± 44	0.69
E_t sevoflurane (vol%)	pre	0.84 ± 0.1	0.85 ± 0.1	0.86
	occ	0.84 ± 0.1	0.84 ± 0.1	0.85
Hgb (g/dl)	pre	13.1 ± 2	12.7 ± 1	0.50
	occ	13.1 ± 2	12.7 ± 1	0.58
$T_{esophageal}$ (°C)	pre	35.7 ± 0.6	35.4 ± 0.5	0.13
	occ	35.7 ± 0.6	35.4 ± 0.5	0.20

Data were recorded at the time of the preocclusion (pre) and occlusion (occ) rCBF determinations.

vol% administered in a 50% mixture of oxygen and nitrous oxide provided an EEG tracing adequate for the detection of cerebral ischemia. The EEG signal under these conditions was also remarkably stable, showing little response to changing levels of surgical stimulus. The ability of the EEG to detect ischemia under these conditions is supported by the fact that all cases of cross-clamp-induced ischemic EEG changes were promptly reversed by shunt placement.

The $rCBF_{50}$ determined for patients anesthetized with sevoflurane and N_2O is similar to the 8-10 ml · 100 $g^{-1} \cdot min^{-1}$ reported by Messick *et al.*[3] and the 10 ml · 100 $g^{-1} \cdot min^{-1}$ reported by Michenfelder *et al.*[4] as the critical rCBF for patients anesthetized with isoflurane. It may be inappropriate to compare the critical rCBF values of sevoflurane and isoflurane because they were not studied contemporaneously in a randomized, prospective manner. Changes in patient population and in anesthetic and surgical techniques have occurred in the decade elapsed between this study and the determination of the isoflurane critical rCBF. Such changes may be confounding variables when historical comparisons are being made.

In Messick *et al.*'s[3] study of 31 patients undergoing carotid endarterectomy with isoflurane anesthesia, all 6 patients in whom EEG changes developed had rCBF values <10 ml · 100 $g^{-1} \cdot min^{-1}$. Using his definition that the critical rCBF was the "flow below which EEG signs of cortical ischemia occurred," he concluded that the critical rCBF of isoflurane was 8-10 ml · 100 $g^{-1} \cdot min^{-1}$.[3] Michenfelder *et al.*,[4] on the other hand, retrospectively analyzed the records of 703 patients undergoing carotid endarterectomy with isoflurane anesthesia and determined that, of the 126 patients who had EEG changes, those changes developed at a rCBF of 10-14 ml · 100 $g^{-1} \cdot min^{-1}$ in 36 patients, and 10 patients showed changes at 15-19 ml · 100 $g^{-1} \cdot min^{-1}$. The results of Messick *et al.*[3] did not predict the 46 patients in whom EEG changes developed with rCBF values >10 ml · 100 $g^{-1} \cdot min^{-1}$. Conversely, application of Messick *et al.*'s definition of critical rCBF ($rCBF_{100}$) to the larger, retrospective series of patients results in a critical rCBF of 15-19 ml · 100 $g^{-1} \cdot min^{-1}$ but <20 ml · 100 $g^{-1} \cdot min^{-1}$ for isoflurane. We propose that the relation between rCBF and the probability of no carotid cross-clamp-related ischemic EEG change is best described using logistic regression analysis. Showing the entire logistic regression curve permits estimation of $rCBF_x$ and the confidence interval in $rCBF_x$ and underscores the fact that there is no single rCBF value below which all EEG tracings demonstrate ischemia and above which all tracings are ischemia-free. The critical rCBF is best described as a range of rCBF values rather than as a single rCBF value, over which carotid cross-clamp-related ischemic EEG changes occur in a population. Because the $rCBF_{50}$ is most analogous to the previous definition of critical rCBF used by Michenfelder *et al.*,[4] we suggest that the critical rCBF could be operationally defined as $rCBF_{50} \pm SD$, the rCBF at which 50% of patients undergoing carotid endarterectomy will have cross-clamp-related ischemic EEG changes.

In conclusion, we found in this study that EEG monitoring for cerebral ischemia is feasible with 0.6-1.2% sevoflurane administered in 50% nitrous oxide. Further, we have analyzed the correlation between rCBF and EEG change using logistic regression analysis. This makes it possible to determine the $rCBF_x$ and the standard deviation in $rCBF_x$ from the slope and intercept values in the logistic regression curve and the variance in these values. Logistic regression analysis also permits rigorous comparison of $rCBF_x$ as a function of other variables, such as anesthetic agent or patient temperature. Using this analysis, we determined that the $rCBF_{50}$ of sevoflurane is 11.5 ± 1.4 ml · 100 $g^{-1} \cdot min^{-1}$, a result similar to that previously determined by other analytic methods in patients anesthetized with isoflurane.

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References

1. Sharbrough FW, Messick JM Jr, Sundt TM Jr: Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. Stroke 1973; 4:674-83

2. Sundt TM Jr, Sharbrough FW, Piepgras DG, Kearns TP, Messick JM Jr, 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; 56:533-43

3. Messick JM Jr, Casement B, Sharbrough FW, Milde LN, Michenfelder JD, Sundt TM Jr: Correlation of regional cerebral blood flow (rCBF) with EEG changes during isoflurane anesthesia for carotid endarterectomy: Critical rCBF. ANESTHESIOLOGY 1987; 66:344-9

4. Michenfelder JD, Sundt TM, Fode N, Sharbrough FW: Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. ANESTHESIOLOGY 1987; 67:336–40

5. Stern RC, Towler SC, White PF, Evers AS: Elimination kinetics of sevoflurane and halothane from blood, brain, and adipose tissue in the rat. Anesth Analg 1990; 71:658–64

6. Eger EI II, Johnson BH: Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987; 66:977–82

7. Smith I, Ding Y, White PF: Comparison of induction, maintenance, and recovery characteristics of sevoflurane-N_2O and propofol-sevoflurane-N_2O with propofol-isoflurane-N_2O anesthesia. Anesth Analg 1992; 74:253–9

8. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. ANESTHESIOLOGY 1981; 54:100–6

9. Kanno I, Uemura K: Some experimental errors in calculating regional cerebral blood flow from the intracarotid 133Xe clearance curve. Stroke 1975; 6:370–75

10. Waud D: On biological assays involving quantal response. J Pharmacol Exp Ther 1972; 183:577–607