Evaluation of a Cerebral Oximeter as a Monitor of Cerebral Ischemia during Carotid Endarterectomy

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Background: Stroke is an important contributor to perioperative morbidity and mortality associated with carotid endarterectomy (CEA). This investigation was designed to compare the performance of the INVOS-3100 cerebral oximeter to neurologic function, as a means of detecting cerebral ischemia induced by carotid cross-clamping, in patients undergoing carotid endarterectomy with cervical plexus block.

Methods: Ninety-nine patients undergoing 100 CEA s with regional anesthesia (deep or superficial cervical plexus block) were studied. Bilateral regional cerebrovascular oxygen saturation (rSO2) was monitored using the INVOS-3100 cerebral oximeter. Patients were retrospectively assigned to one of two groups: those in whom a change in mental status or contralateral motor deficit was noted after internal carotid clamping (neurologic symptoms; n = 10) and those who did not show any neurologic change (no neurologic symptoms; n = 90). Data from 94 operations (neurologic symptoms = 10 and no neurologic symptoms = 84) were adequate for statistical analyses for group comparisons. A relative decrease in ipsilateral rSO2 after carotid occlusion (calculated as a percentage of preoclusion value) during all operations (n = 100) was also calculated to determine the critical level of rSO2 decrease associated with a change in neurologic function.

Results: The mean (± SD) decrease in rSO2 after carotid occlusion in the neurologic symptoms group (from 63.2 ± 8.4% to 51.0 ± 11.6%) was significantly greater (P = 0.0002) than in the no neurologic symptoms group (from 65.8 ± 8.5% to 61.0 ± 9.3%). Logistic regression analysis used to determine if a change in rSO2, calculated as a percentage of preclamp value, could be used to predict change in neurologic function was highly significant (likelihood ratio chi-square = 13.7; P = 0.0002). A 20% decrease in rSO2, reading from the preclamp baseline, as a predictor of neurologic compromise, resulted in a sensitivity of 80% and specificity of 82.2%. The false-positive rate using this cutoff point was 66.7%, and the false-negative rate was 2.6%, providing a positive predictive value of 33.3% and a negative predictive value of 97.4%.

Conclusion: Monitoring rSO2 with INVOS-3100 to detect cerebral ischemia during CEA has a high negative predictive value, but the positive predictive value is low. (Key words: Cerebral oximetry; near-infrared spectroscopy.)

RECENT multicenter trials1–5 have clearly established that carotid endarterectomy (CEA) is beneficial in symptomatic as well as asymptomatic patients with high-grade and moderate carotid stenoses. Nevertheless, perioperative stroke occurs in 2–3% of patients undergoing CEA,5–5 usually caused by either cerebral ischemia or embolism during surgery. Routine insertion of a shunt to prevent or minimize cerebral ischemia may increase the likelihood of stroke caused by embolism. It is therefore important to identify patients who are at risk for developing cerebral ischemia during carotid occlusion and who are likely to benefit from shunting, before insertion of a shunt. Despite several existing monitoring methods, the assessment of cerebral ischemia during CEA has been unreliable5,6 in predicting perioperative stroke. New monitoring modalities need to be evaluated.

Cerebral oximetry, based on the principles of near-infrared spectroscopy as first described by Jobsis,7 is a noninvasive technique to monitor cerebral oxygenation. Although this technique was described nearly two decades ago, the instrumentation to make it a clinically useful monitor is still being perfected. Early clinical investigations with this technology used prototype instruments. Recent research has been devoted to the development of an instrument that is more simple to use. This has resulted in the introduction of a commercially available cerebral oximeter, INVOS 3100 (Somanetics Corp., Troy, MI). Several validation studies using this cerebral oximeter to monitor brain oxygenation during conditions of hypoxemia, hypercapnia, and hypocapnia in awake volunteers have been published.8,9 Concerns regarding the inability of this monitor to eliminate contamination from extracranial tissues were raised by early studies.10,11 More recent clinical investigations12,13 have suggested that INVOS-3100 primarily tracks changes in intracranial circulation. However, the ability of this monitor to detect acute cerebral ischemia in humans has not been fully investigated. The majority of clinical investigations with this cerebral oximeter have been conducted in patients during general anesthesia during CEA and deep hypothermic circulatory arrest. Performance of this device as a monitor of cerebral ischemia has been compared with other means of assessing cerebral ischemia such as electroencephalography,14 somatosensory evoked potentials (SSEPs),15 transcranial Doppler, and measurements of jugular bulb venous oxygen saturation.16,17 All of these monitors provide indirect evidence of cerebral ischemia and have been used to guide decision for shunt insertion, but their dependability in pre-
dicting neurologic outcome has not been systematically investigated.

The present study was designed to evaluate the performance of the INVOS-3100 cerebral oximeter to detect development of cerebral ischemia during carotid artery cross-clamping, as evidenced by changes in mental status or development of motor deficits in awake patients undergoing CEA with regional anesthesia.

**Methods**

Ninety-nine adults (51 men, 48 women) between the ages of 43 and 90 yr who underwent 100 CEAs over a 4-yr time period were studied. All patients gave informed consent to participate in the study according to the guidelines approved by the Institutional Review Board of the University of Michigan Health System. All patients were scheduled to undergo CEA with regional anesthesia by one of three attending vascular surgeons. All patients had high-grade carotid artery stenoses (> 70%) documented by preoperative carotid duplex sonography.

An ipsilateral cervical plexus block (superficial or deep) was performed using 0.375% bupivacaine. A radial artery was cannulated for continuous monitoring of blood pressure. Electrocardiogram (lead V5), peripheral hemoglobin saturation, and regional cerebrovascular saturation (rSO2) were continuously monitored during operation. Two cerebral oximeters (model INVOS-3100) were used for simultaneous, bilateral rSO2 monitoring. Details of the principles of cerebral oxymetry used by INVOS-3100 have been described in a previous report. This oximeter monitors only changes in cerebral oxygen saturation from an unknown baseline, recording those as numerical values of rSO2 index. INVOS-3100 is thus suitable as a trend monitor only.

The cerebral oximeter sensors were applied to the forehead, one on either side of the midline, such that the light transmitters were placed at least 3 cm from the midline. The sensors were covered with an adhesive cover to shield them from ambient light. Adhesive tape was used to hold the sensors firmly in place and assure contact with skin throughout the operation. The numerical rSO2 readings recorded at 1-min intervals were stored on computer disks for offline data analysis at a later time. The signal average time for each numerical value was 4 s.

Minimal sedation with 1–2 mg midazolam, administered intravenously, was used before performing the cervical plexus block in a preoperative holding room approximately 30 min before the skin incision. After all monitoring was established, surgery proceeded with an approximately 30 min before the skin incision. After all cervical plexus block in a preoperative holding room terminated intravenously, was used before performing the time for each numerical value was 4 s.

For offline data analysis at a later time. The signal average time for each numerical value was 4 s.

Thus, a change of rSO2 reading from a mean preclamp value of 70% saturation to a minimal (after cross-clamp) reading during cross-clamp periods in each patient accounts for 5% decrease in rSO2 reading.

**Statistical Analysis**

The phase of operation (preclamp, cross-clamp, and postclamp), side of measurement (ipsilateral and contralateral), and group designation (neurologic symptoms vs. no neurologic symptoms) effect on mean rSO2 values were studied using three-way repeated-measures analysis of variance. Numerical data for rSO2 from the 10 CEAs in which a change in neurologic function, the rSO2 data were normalized by calculating a percentage change in rSO2 reading during cross-clamp periods in each patient according to the formula:

\[\text{Percent change} = \left(\frac{\text{mean rSO}_2 \text{ reading preclamp} - \text{minimum rSO}_2 \text{ reading cross-clamp}}{\text{mean rSO}_2 \text{ reading preclamp}}\right) \times 100\]

Thus, a change of rSO2 reading from a mean preclamp value of 70% saturation to a minimal (after cross-clamp) of 63% saturation according to this formula would represent a 10% decrease in rSO2 reading.

**Regional Cerebrovascular Oxygen Saturation Data Analysis**

The duration of the CEA procedure was divided into three phases: (1) preclamp: from skin incision to carotid occlusion; (2) cross-clamp: from carotid artery clamp application to clamp release; and (3) postclamp: from clamp removal to skin closure. Mean values of rSO2 for preclamp, cross-clamp, and postclamp phases for each hemisphere in each patient were calculated from the readings recorded at 1-min intervals. After completion of the study, patients were assigned to one of two groups: those who did not show a change in neurologic function (no neurologic symptoms, n = 90), and those who did (neurologic symptoms, n = 10). Intersubject variability in rSO2 index values is well known and was noticed in this study. To facilitate comparison of rSO2 changes after carotid cross-clamp among all patients, and to determine the magnitude of rSO2 change that was associated with a change in neurologic function, the rSO2 data were normalized by calculating a percentage change in rSO2 reading during cross-clamp periods in each patient according to the formula:

\[\text{Percent change} = \left(\frac{\text{mean rSO}_2 \text{ reading preclamp} - \text{minimum rSO}_2 \text{ reading cross-clamp}}{\text{mean rSO}_2 \text{ reading preclamp}}\right) \times 100\]

Thus, a change of rSO2 reading from a mean preclamp value of 70% saturation to a minimal (after cross-clamp) of 63% saturation according to this formula would represent a 10% decrease in rSO2 reading.
erations in the no neurologic symptoms group were incomplete or not retrievable because of defective data disks. Raw data (rather than normalized percentage change) for rSO2 values were used for the analysis of variance. Phase and side were included in the model as within-subjects effects and group as a between-subjects effect. Because of unequal variances that were observed for the neurologic symptoms and no neurologic symptom groups, the repeated-measures analysis of variance incorporated this feature. All post hoc comparisons were performed using the Tukey-Kramer adjustment for multiple comparisons. A Wilcoxon rank sum nonparametric test was used to compare the two groups for the duration of cross-clamp, because it could not reasonably be assumed to be normally distributed.

Normalized data from ipsilateral hemispheres from all operations (n = 100) were subjected to logistic regression analysis to determine if it was possible to estimate the probability of change in neurologic function, based on a decrease in rSO2 during cross-clamp relative to the mean rSO2 reading during the preclamp phase. Sensitivity and specificity, false-positive rate and false-negative rate, as well as the positive and negative predictive value of a 20% relative decrease in rSO2 as a predictor of cerebral ischemia were calculated. The SAS statistical software package (Proprietary software release 6.12, SAS Institute, Inc., Cary NC) was used for statistical analyses.

Results

Carotid endarterectomy was successfully completed with regional anesthesia in all patients. No neurologic change was observed in 90 operations, whereas neurologic changes occurred in 10 operations after carotid clamping. Neurologic change resolved after insertion of an intravascular shunt in seven of these patients. In the three remaining patients who developed a neurologic change, the surgeon anticipated a very short clamp time and elected to complete the operation without use of a shunt. Data from all 10 patients with neurologic changes, including the three latter patients, were included in the neurologic symptoms group for statistical analyses.

Ninety-seven patients left the hospital without a clinically detectable, new neurologic deficit. One patient who had no intraoperative problems (no neurologic symptoms group), developed significant hemodynamic instability in the postoperative period, necessitating insertion of a pulmonary artery catheter, and subsequently died. Another patient, an 80-yr-old woman (neurologic symptoms group) developed hemiplegia. She presented with symptomatic high-grade stenosis of right internal carotid artery and evidence of generalized cerebral atrophy on magnetic resonance imaging. Bilateral rSO2 readings were within normal limits during the preclamp period but after occlusion of carotid artery, ipsilateral

Fig. 1. Time course of changes in cerebrovascular oxygen saturation in one patient. This patient became aphasic, apneic, and unresponsive within 2 min after carotid cross-clamp. Almost mirror-image changes were noted on the contralateral hemisphere.
rSO$_2$ value decreased by 29.3% (from 55 to 39) within 2 min (fig. 1). The patient became aphasic, unresponsive, and apneic, resulting in intravascular shunt being quickly inserted. One minute later, the patient responded to verbal commands, and the rSO$_2$ increased to mid-40s and remained at that level as the CEA was completed. She developed severe hypotension after administration of protamine, which progressed to cardiac electromechanical dissociation necessitating endotracheal intubation and cardiopulmonary resuscitation as the skin incision was being closed. On awakening, the patient had decreased responsiveness to verbal commands and developed left hemiplegia. A computed tomography scan revealed an ischemic infarct in the right hemisphere in the watershed distribution between ipsilateral anterior and middle cerebral as well as between the middle and posterior cerebral arteries.

The numerical values (mean ± SD) for duration of cross-clamp and rSO$_2$ for 94 patients, with bilateral monitoring in the three phases of operation are shown in table 1. The duration of cross-clamp time was longer in neurologic symptoms group, but this difference was not statistically significant. There was no significant difference between the two groups when either ipsilateral or contralateral values of rSO$_2$ during the three phases were compared. Results of pairwise comparisons of interest from this analysis were revealing (table 2). There were no significant changes in rSO$_2$ in the contralateral hemispheres in either group. However, on the ipsilateral side in both groups there was a significant decrease in rSO$_2$ during the cross-clamp phase when compared with the preclamp and postclamp phases. The decrease in rSO$_2$ from the preclamp to cross-clamp period on the ipsilateral side was significantly greater (12.2% vs. 4.8%, P = 0.0001) in the neurologic symptoms group. The change from preclamp to cross-clamp period (2.2% decrease vs. 1.7% increase) on the contralateral side between the two groups was also significant (P = 0.04).

The relative decrease (percent change from mean preclamp value of rSO$_2$) observed after carotid occlusion in

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<th>Table 1. Duration of Cross-clamp, Ipsilateral, and Contralateral Values of rSO$_2$</th>
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<td><strong>Group (n)</strong></td>
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<tr>
<td>No neurologic symptoms (84)</td>
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<td>Neurologic symptoms (10)</td>
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<td>$P$ value</td>
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Duration of cross-clamp, ipsilateral, and contralateral values (mean ± SD) of rSO$_2$ observed during preclamp, cross-clamp and postclamp phases. Statistical methods used were Wilcoxon rank-sum test for duration of cross-clamp and repeated measures analysis of variance for rSO$_2$ values. rSO$_2$ = regional cerebrovascular oxygen saturation.

<table>
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<th>Table 2. Comparisons of Interest</th>
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<td><strong>Group/Side</strong></td>
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<td>No neurologic symptoms (n = 90)</td>
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<td>Contralateral</td>
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<td>Neurologic symptoms (n = 10)</td>
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<td>Neurologic symptoms vs. no neurologic symptoms</td>
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<td>Contralateral</td>
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<td>Ipsilateral</td>
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Results of three-way repeated measures analysis of variance showing differences between the two groups and two sides during various phases of operation in 94 patients.

* Significant difference at 0.05 using Tukey-Kramer adjustment for multiple comparison.

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100 operations is shown in figure 2. A logistic regression analysis was used to determine if a change in rSO2 (relative decrease) after carotid occlusion could be used to predict development of neurologic deterioration. It was decided to determine a reasonable cutoff point and calculate the sensitivity and specificity of this cutoff point. This logistic regression was highly significant (likelihood ratio chi-square = 13.7, 1 df, \(P = 0.0002\)). The sensitivity and specificity of several cutoff points were analyzed based on the logistic regression model probabilities. The model probability for the best cutoff point was then translated back into the corresponding decrease in rSO2. A cutoff point of 20% relative decrease in rSO2 gave the best sensitivity and specificity results. This cutoff value resulted in a sensitivity of 80% (8 of 10 patients who developed a neurologic change had rSO2 decrease > 20%, whereas two did not). The specificity of this cutoff point was 82.2% (74 of the 90 patients who did not develop a neurologic change had < 20% relative decrease of rSO2, whereas in 16 patients rSO2 decrease was > 20%). The false-positive rate for this cutoff was 66.7% (16 of the 24 patients predicted to develop neurologic dysfunction based on the cutoff did not develop one) and a false-negative rate of 2.6% (2 of 76 patients who were predicted to not develop neurologic dysfunction actually did develop one). The positive-negative predictive values of a 20% decrease in rSO2 (compared with preclamp value) were calculated as 97.4% negative predictive value (74 of the 76 patients with < 20% decrease did not show neurologic deterioration) and a 33.3% positive predictive value (only 8 of 24 patients with > 20% decrease developed a neurologic change).

**Discussion**

This study was designed to evaluate the performance of the INVOS-3100 cerebral oximeter to detect development of cerebral ischemia. Clinical signs of cerebral ischemia developed during 10 operations and were temporally related to occlusion of internal carotid artery. An intravascular shunt was used in seven of these patients, whereas surgery was completed without shunt in three in whom a brief period of occlusion was anticipated. No postoperative, new neurologic deficit developed in any of these three patients, demonstrating that a short period of cerebral ischemia may be tolerated without permanent sequelae.

The intersubject variability of rSO2 values in the preclamp period and variable decreases in rSO2 observed...
after cross-clamp in the current study is in agreement with that reported in previous studies.\textsuperscript{18,19} The change in rSO\textsubscript{2} after cross-clamp was significantly greater in patients who developed neurologic symptoms when compared with those who did not. This finding is in agreement with a recent study comparing cerebral oximetry with changes in amplitude of SSEPs during CEA in 29 patients.\textsuperscript{15} Cho et al.\textsuperscript{15} reported that the decrease in rSO\textsubscript{2} was greater than 10 units in patients who showed a significant decrease in SSEP amplitude and ranged between −2 and −6.1 units in those who did not have a significant change in SSEPs. They concluded that a decrease of > 10 units or an rSO\textsubscript{2} reading < 50 (as measured by INVOS-3100) is indicative of cerebral ischemia. The magnitude of the mean decrease in rSO\textsubscript{2} in the current study (4.8 units in patients without neurologic dysfunction and 12.2 units in those with neurologic dysfunction) was similar.

The intersubject variability in rSO\textsubscript{2} index could be addressed by normalizing the data and recording the decrease in rSO\textsubscript{2} after cross-clamp as a percentage of preclamp value. Such normalization will not only account for intersubject variability but will also allow comparisons between different investigations.

Data from the current investigation revealed that the use of rSO\textsubscript{2} monitoring and percentage change in rSO\textsubscript{2} after cross-clamp to predict development of neurologic deficit has significant limitations. In this study, observed rSO\textsubscript{2} values were similar in the two groups in all three phases of operation (table 1). On post hoc analysis, the difference in ipsilateral rSO\textsubscript{2} decrease after carotid occlusion was significantly greater in patients in the neurologic symptoms group. However, within subjects, a cutoff point of 20% decrease from preclamp value, which provided the best sensitivity (80%) and specificity (82.2%) in awake patients, had a negative predictive value of 97.4% and a positive predictive value of only 33.3%. There are several possible explanations for false-negative and false-positive results in our study: (1) the sensors of cerebral oximeter were applied to the hairless scalp overlying the frontal lobe, whereas the most vulnerable area of brain for ischemia–embolism is in the distribution of middle cerebral artery. The cerebral blood flow changes are heterogeneous in nature, and ischemia may develop in parietal lobes (distribution of middle cerebral artery) without a simultaneous change in rSO\textsubscript{2} monitored over the region of frontal lobes. (2) The neurologic examination was crude and limited (for practical reasons) and might have missed evidence of cerebral ischemia. (3) There was variable contribution of extracranial circulation to monitored rSO\textsubscript{2}.

A comparison of rSO\textsubscript{2} monitoring with other currently accepted monitors of cerebral ischemia is desirable but difficult to achieve because an intervention (insertion of shunt) is generally made whenever monitoring suggests development of cerebral ischemia in anesthetized patients. Only a few studies have determined sensitivity and specificity of different monitoring modalities using development of stroke as primary outcome variable. Blume et al.\textsuperscript{20} have evaluated the significance of electroencephalography changes in 176 patients undergoing CEA with general anesthesia, in whom a shunt was not inserted even if electroencephalography changes were observed. They had no false-negative results but had a 90.9% false-positive rate (only 2 of 22 patients predicted to require a shunt actually had a stroke). Lam et al.\textsuperscript{21} compared the sensitivity and specificity of electroencephalography and SSEPs as a monitor of cerebral ischemia in 67 patients during CEAs with general anesthesia, without use of a shunt, even if electroencephalography or SSEP changes were observed. They concluded that the relative sensitivity and specificity for electroencephalography and SSEPs in detecting postoperative stroke (without any intervention) was 50% and 92% for electroencephalography and 100% and 94% for SSEPs, respectively. However, our findings cannot be directly compared with these studies because different end points (temporary ischemia vs. stroke) were used.

When compared with intraoperative electroencephalography and SSEP monitoring, rSO\textsubscript{2} monitoring has the advantages of being easy to use and less expensive. One major limitation in accepting rSO\textsubscript{2} as a replacement for electroencephalography and SSEP monitoring is that changes in electroencephalography and SSEPs have been shown to correlate directly with changes in cerebral blood flow,\textsuperscript{22–24} whereas no such data for rSO\textsubscript{2} are currently available. The evidence that rSO\textsubscript{2} corresponds with changes in cerebral blood flow is indirect, provided by studies correlating changes in electroencephalography, SSEPs, and transcranial Doppler, with those in rSO\textsubscript{2}.\textsuperscript{14–16,19}

The results of the current investigation, which suggest a 20% relative decrease in rSO\textsubscript{2} as a predictor of cerebral ischemia, are comparable to those recently reported in a study by Roberts et al.\textsuperscript{25} They monitored 45 patients undergoing 50 CEAs with regional anesthesia. In their study, four patients who required a shunt had a > 27% decrease in rSO\textsubscript{2} after carotid cross-clamp, and in the remaining 41 patients the rSO\textsubscript{2} decrease varied between 0% and 23%. They suggested that a decrease of ≥ 27% in rSO\textsubscript{2} should suggest the need for a shunt, and a decrease < 27% should not require a shunt. In other words, they did not have any false-positive or false-negative results. In our study, using a 20% decrease as the cutoff point, we had a false-negative rate of 2.6% and a false-positive rate of 66.7%. A possible explanation for this difference is that the duration of cross-clamp was shorter in their study. Patients may tolerate cerebral ischemia of short duration without clinical development of neurologic symptoms. Three patients in our study who developed neurologic symptoms and completed surgery without a shunt had short clamp times and did...
not have any permanent sequelae, clearly demonstrating that it is a combination of both the magnitude and duration of ischemia that leads to neurologic deficit.

One of the limitations of currently available technology is that the sensors are applicable only to the skin devoid of hair follicles. Development of sensors that can be applied to the scalp overlying the area of distribution of middle cerebral artery and monitoring from multiple sensors may further improve the performance of this cerebral oximeter as a monitor of cerebral ischemia.

In conclusion, this investigation suggests that a change in \( rSO_2 \) after carotid cross-clamp during CEA can be used as a trend monitor for predicting development of cerebral ischemia only to a limited extent. It is not possible to specify an absolute \( rSO_2 \) reading as the critical value below which cerebral ischemia may develop. A relative decrease of \( \approx 20\% \) (from the preclamp \( rSO_2 \) values) after carotid occlusion has a high negative predictive value, \( i.e. \), if \( rSO_2 \) does not decrease, ischemia is unlikely, but a low positive predictive value, \( i.e. \), a decrease in \( rSO_2 \) may not always indicate cerebral ischemia. When used in this manner, \( rSO_2 \) monitoring has a sensitivity and specificity similar to electroencephalography and SSEP monitoring with a low (2.6\%) false-negative rate but high (66.7\%) false-positive rate. Development of oximeter sensors that can be applied to the scalp over the parietal region may further enhance the clinical utility of this monitoring technique.

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