Electroencephalography and Brain Oxygenation Monitoring in the Perioperative Period

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Maintaining brain function and integrity is a pivotal part of anesthesiological practice. The present overview aims to describe the current role of the 2 most frequently used monitoring methods for evaluation brain function in the perioperative period, ie, electroencephalography (EEG) and brain oxygenation monitoring. Available evidence suggests that EEG-derived parameters give additional information about depth of anesthesia for optimizing anesthetic titration. The effects on reduction of drug consumption or recovery time are heterogeneous, but most studies show a reduction of recovery times if anesthesia is titrated along processed EEG. It has been hypothesized that future EEG-derived indices will allow a better understanding of the neurophysiological principles of anesthetic-induced alteration of consciousness instead of the probabilistic approach most often used nowadays.

Brain oxygenation can be either measured directly in brain parenchyma via a surgical burr hole, estimated from the venous outflow of the brain via a catheter in the jugular bulb, or assessed noninvasively by near-infrared spectroscopy. The latter method has increasingly been accepted clinically due to its ease of use and increasing evidence that near-infrared spectroscopy–derived cerebral oxygen saturation levels are associated with neurological and/or general perioperative complications and increased mortality. Furthermore, a goal-directed strategy aiming to avoid cerebral desaturations might help to reduce these complications. Recent evidence points out that this technology may additionally be used to assess autoregulation of cerebral blood flow and thereby help to titrate arterial blood pressure to the individual needs and for bedside diagnosis of disturbed autoregulation. (Anesth Analg 2019;128:265–77)

EEG-DERIVED BRAIN FUNCTION MONITORING

Various monitoring techniques have become available to monitor the functional activity of the brain. Investigators have focused mainly on the capability of several brain-monitoring techniques to measure the hypnotic and analgesic component of general anesthesia. Because the brain is the main target organ of general anesthesia and the EEG provides information on (spontaneous electrical) cortical activity, the information obtained by the EEG can be used as a surrogate measure of hypnosis.3,4 However, the EEG trace is complex and most clinicians are inexperienced encephalographers. Therefore, since the mid-1990s, a variety of EEG-derived indices has been introduced to aid the clinician in analyzing this information, with thebispectral index (BIS) as the most widely known and used index. EEG-derived indices are nowadays frequently used to improve perioperative anesthetic titration. Nevertheless, studies concerning the influence of EEG-derived indices on patient outcomes are inconclusive. This review aims to describe the available technologies for brain function monitoring and to detail their indications, comparability, and limitations.

EEG-Derived Indices

The number of commercially available EEG-derived indices (measuring the hypnotic component) is still growing; using comparable principles, but especially differing regarding the algorithms used. These indices generally have a scaled index ranging between 100 and 0, where 100 represents “awake state” and 0 represents “no detectable brain electrical activity,” inversely correlated with the hypnotic drug concentration. The most commonly used and reviewed indices are the BIS (Medtronic, Boulder, CO), the E-Entropy (GE Healthcare, Helsinki, Finland), and the Narcotrend (Narcotrend Gruppe, Hannover, Germany), followed by the Patient State Index (SEDline, Masimo Corp, Irvine, CA) and the NeuroSense (WAV CNS, NeuroWave Systems Inc, Cleveland Heights, OH).

Monitoring techniques measuring the analgesic component of anesthesia, the balance between nociception and antinociception, is the most recent development in this field. Indices measuring this component are the qCON/
qNOX (Quantium Medical, Barcelona, Spain),

The influence of index-guided anesthesia on drug consumption, emergence, and early recovery compared to routine care is an ongoing debate, with many studies showing an improvement in these outcomes, while others found no substantial effect. However, the authors of the latest Cochrane review concluded that, regardless of the hypnotic drug used, using the BIS could significantly reduce drug consumption, as well as all aspects of the postoperative recovery time. Only the length of hospital stay after ambulatory surgery is not significantly reduced.

Over the past decade, research suggested that deep anesthesia (BIS < 45) is correlated with postoperative mortality. Also a “triple low” state (a combination of low BIS, low blood pressure, and low minimum alveolar concentration), possibly related to anesthetic sensitivity, has been associated with a higher mortality rate. However, these associations are based on post hoc analyses.

Until today, just 1 randomized controlled trial showed a significant association with deep anesthesia and mortality in high-risk patients, and 2 others failed to demonstrate this association. Therefore, an ongoing large prospective randomized controlled trial will further elucidate the influence of anesthetic depth on long-term mortality.

A recent Cochrane review found that BIS is able to reduce the incidence of postoperative delirium compared to routine care. Evidence concerning the role of depth of anesthesia or even anesthesia in causing postoperative cognitive dysfunction (POCD) is still evolving, with conflicting results. Therefore, further research is needed.

Comparability. Because there is no “gold standard” for measuring the depth of anesthesia, indirect parameters must be used to validate and compare EEG-derived indices. To accommodate comparisons between indices, the authors proposed a 5-step validation process to evaluate the different indices, consisting of the validation of the index for detecting clinical signs of anesthesia, pharmacokinetic-dynamic validation (quantifying the correlation between the index and the hypnotic drug concentration), validation of performance under clinical conditions, improving outcome, and a cost-effectiveness analysis. Until now, there is no convincing evidence for superiority of one of the indices over the other.

Limitations. The absolute values of EEG-derived indices have to be interpreted with caution because these indices suffer from a few limitations. The signal of the indices is influenced by a variety of variables other than changes in depth of anesthesia, including neurologic disorders such as dementia, muscle activity, electrical interference, and hypothermia. Moreover, the use of EEG-derived indices is not applicable for every hypnotic drug, such as ketamine and nitrous oxide, because it alters the raw EEG and power spectrum differently through its exertion on different molecular targets and neural pathways than most other hypnotic anesthetics. Because these drug-specific alterations are clearly visible in the raw EEG and power spectrum, it has been advocated to train the anesthesiologist in recognizing these real-time “signatures.” Supporting this opinion is the fact that the burst suppression pattern is readily visible in the raw EEG as well, while most indices

Methodology. EEG-derived indices usually have only 2-4 electrodes placed on the forehead for receiving electrical signals from the (frontal) brain. The EEG signal is amplified, digitized, and filtered for analysis of the EEG trace. Most of the indices assume an underlying mathematical algorithm implying the relation between the electrical activity and the clinical state of arousal of the patient, with high and low frequencies corresponding with the awake state and deep hypnosis, respectively. These algorithms often use a multiparametric approach clustering the analysis of subparameters (eg, time domain, frequency domain, spectrum, and power analysis) of the EEG. Due to variations in algorithms used between indices, every device has its own specific intraoperative target range and absolute index values differ between various commercially available devices. Some indices use a proprietary-protected algorithm and are therefore not entirely published. The published specifications of the algorithms have been reviewed in detail elsewhere.

Indications. As mentioned above, EEG-derived indices are mostly used to improve perioperative anesthetic drug titration, and most indices have been demonstrated to correlate closely with the hypnotic effect of most anesthetic drugs. However, convincing evidence on the influence of EEG-derived indices on patient outcomes is missing due to many confounding factors. Because BIS was the first and is the most widely used monitor, the vast majority of the clinical utility studies has been done with this index.

The prevention of intraoperative awareness is regarded as one of the most important patient outcomes. Awareness is a rare event (1 case/19,600 patients), but could have really distressing consequences. Avidan and Mashour recently reviewed 6 large prospective trials studying the potential benefit of EEG-derived indices in preventing awareness. At first view, these trials gave inconsistent results; however, they concluded that the use of BIS could reduce intraoperative awareness in patients receiving total intravenous anesthesia, but when solely volatile agents are used, following an end-tidal anesthetic concentration titration protocol is as equally effective as a BIS-based protocol. These interpretations are in agreement with the recent conclusions of the Cochrane review concerning this topic.

Significant cerebral ischemia or hypoperfusion during anesthesia can be detected by changes in the EEG. Particularly during stable anesthesia, a sudden alteration in the EEG (ie, shift in power to lower frequency ranges, decrease in amplitude [progressive], periods of burst suppression, or even isoelectricity) and/or a drop in the index value may indicate incidental cerebral ischemia. Nonetheless, a stable, unaltered BIS does not exclude ischemia in other parts of the brain than the frontal area. In all probability, other more specific monitors are more useful to detect cerebral ischemia and hypoperfusion, which will be discussed briefly later in this review.
have difficulties processing this pattern. In addition, the indices only monitor the frontal area of the brain, possibly missing valuable information on changing network relationships between brain regions during anesthesia.\textsuperscript{18,69} Furthermore, indices suffer from a time delay to calculate and display the index value and to process a sudden change in clinical state.\textsuperscript{70} It is therefore suggested not to change titration of anesthesia on absolute values rather than follow a trend analysis instead.

**BRAIN OXYGENATION MONITORING**

Taking a glance at the many tools available for monitoring of the cardiovascular system and comparing this number with the few commercially available systems for brain oxygenation monitoring, one may get the impression that brain integrity and function must be less important than that of heart and vessels. However, this discrepancy can easily be explained by the fact that the assessment of brain oxygenation is far from trivial and that—despite many years of clinical research—cerebral oxygenation monitoring is still an evolving field. This review aims to describe the commonly used technologies for brain oxygenation monitoring and to detail their indications, comparability, and limitations.

**Jugular Bulb Venous Oxygen Saturation**

Jugular bulb oxygen saturation (S\textsubscript{jvO\textsubscript{2}}) is reflective of the global ratio between cerebral oxygen delivery and demand. Technically, S\textsubscript{jvO\textsubscript{2}} is derived from a catheter inserted in the jugular bulb by retrograde cannulation of the internal jugular vein. The positioning of the catheter may be facilitated by ultrasound; however, determination of the correct position in the jugular bulb needs to be performed radiologically due to the proximity of the facial vein which contributes oxygen-rich blood from extracranial tissue that may contaminate the measurements and lead to falsely high levels of S\textsubscript{jvO\textsubscript{2}}.\textsuperscript{71}

Practically, determination of S\textsubscript{jvO\textsubscript{2}} may be accomplished either by intermittent blood sampling or by use of a fiber-optic catheter. As described below, both methods may have relevant technical limitations that need to be taken into account. The technique was first described in humans around 1940 and was increasingly investigated up to the year 2000. However, since then, the scientific interest in clinical state—cerebral oxygenation monitoring is still an evolving field. This review aims to describe the commonly used technologies for brain oxygenation monitoring and to detail their indications, comparability, and limitations.

With respect to the invasive nature of this monitoring modality, only sparse data on normal S\textsubscript{jvO\textsubscript{2}} values have been published, despite a variety of studies that used determination of S\textsubscript{jvO\textsubscript{2}} in healthy volunteers for calibration purposes of cerebral oximeters (see below). The available studies give highly variable results for S\textsubscript{jvO\textsubscript{2}} values (about 60.7\% ± 3.6\%), and especially for values in the lower range (with a lower limit [95\% confidence interval] of 44.7 [36.5–53.0]%).\textsuperscript{72} S\textsubscript{jvO\textsubscript{2}} levels below 55\% have repeatedly been associated with poor neurological outcome.\textsuperscript{73} However, there is also evidence that—at least in patients with traumatic brain injury (TBI)—secondary brain damage occurs only if S\textsubscript{jvO\textsubscript{2}} is below 45\%.\textsuperscript{74}

**Indications.** Comparably to direct brain tissue oxygenation, monitoring of S\textsubscript{jvO\textsubscript{2}} has been, and continues to be used in patients with TBI to optimize cerebral oxygen delivery, frequently in combination with other monitoring modalities like intracranial pressure (ICP)/cerebral perfusion pressure (CPP) monitoring.\textsuperscript{75} Additionally, this variable has been used perioperatively in clinical situations during which evaluation of CMRO\textsubscript{2} is necessary, ie, in patients undergoing major thoracic vascular surgery with deep hypothermic circulatory arrest.\textsuperscript{76}

Clinical evidence from randomized trials supporting the use of S\textsubscript{jvO\textsubscript{2}} for optimizing cerebral oxygen balance and guiding therapy for lowering increased ICP in neurocritical care is sparse. Consequently, current expert recommendations\textsuperscript{77} regarding the use of S\textsubscript{jvO\textsubscript{2}} are mostly based on low quality of evidence with the exception of the statement, that “S\textsubscript{jvO\textsubscript{2}}-based therapy (using higher mean arterial blood pressure (MAP)/CPP and optimized volume management to augment CBF) does not improve outcome of severe TBI patients and therefore should not be used alone after TBI (high quality of evidence).” Despite this, the authors recommend that in “patients with severe TBI, abnormal S\textsubscript{jvO\textsubscript{2}} and arterial and jugular venous oxygen content are useful physiological markers associated with poor prognosis (increased mortality, lower Glasgow outcome scale score) when used with other clinical and physiologic data (low quality of evidence).”\textsuperscript{77}

Similarly to the situation in neurocritical care, sparse data are available on the use of S\textsubscript{jvO\textsubscript{2}} for guiding therapy in the perioperative setting. However, some lines of evidence suggest an association between low S\textsubscript{jvO\textsubscript{2}} levels and an increased rate of POCD.\textsuperscript{78}

**Limitations.** Despite the concept of S\textsubscript{jvO\textsubscript{2}} monitoring for assessing global cerebral oxygen balance and (indirectly) CBF seems to be straightforward and physiologically sound, this monitoring technology has some important limitations that not only question its clinical use, but also its fundamental role for calibrating cerebral oximeters (see below).

First, the assumption that cerebral venous effluent is bihemispherically comparable has been challenged. Almost 20 years ago, clinically relevant differences in S\textsubscript{jvO\textsubscript{2}} in neurocritical care patients between the right and the left side have been shown.\textsuperscript{79} In 18\% of patients, the difference was higher than 10\%, and in 15\% of patients even higher than 15\% absolute. Moreover, some patients showed dynamic changes in S\textsubscript{jvO\textsubscript{2}} leading to an even higher (more than 20\%) difference, observations that clearly question the clinical usefulness of this monitoring.

As a second point, due to the proximity of the jugular bulb and the facial vein (draining relatively oxygen-rich
extracranial blood into the jugular vein), even slightest deviations from the optimal catheter position may impair SvO₂ measurements. Taking into account interindividual variability in anatomy, it is on the one hand hard to imagine that it is always possible to position a catheter precisely based on a simple lateral head x-ray and on the other hand rather likely to assume that the catheter will always stay where it was positioned initially during the clinical care of a neurocritical patient.

Additionally, on intermittent blood sampling, contamination with blood from the facial vein may occur if blood is withdrawn too rapidly (faster than 2 mL/min). Likewise, if SvO₂ is measured continuously with a fiberoptic catheter, wall artifacts may lead to erroneous measurements.

As a last but important point, as depicted above, mean normal ranges for SvO₂ have been reported to be in a range between 57.1% and 64.3% with a lower limit of 44.7%. This questions recent expert recommendations suggesting that a “SvO₂ <55% can be considered as the threshold for abnormality and to start intervention.”

Cerebral Oxygen Saturation Determined by Near-Infrared Spectroscopy

Cerebral regional tissue oxygen saturation by near-infrared spectroscopy (NIRS) is the most recent development for bedside monitoring of brain oxygenation and increasingly used in various clinical settings. A growing number of cerebral oximeters is commercially available, using comparable principles, but differing regarding the technology of light emitters, sensors, wavelength, and the algorithms used. The information on brain oxygenation derived by this technology—thus the term regional cerebral (tissue) oxygen saturation ([rSc(t)O₂] or simply ScO₂)—is in between the strictly local and is located between the wavelengths of the visible and infrared light. The physical background is based on absorption analysis of light traveling through biological material according to the Beer-Lambert law. Near-infrared light is characterized by excellent tissue penetration (including bone tissue), allowing measurements of microvascular (<100 µm) hemoglobin oxygen saturation in deeper tissue layers (depending on the distance between light-emitting and light-receiving electrode), even though the skull. Whereas first versions used the transcranial illumination approach, current technology relies on reflection techniques, in which the near-infrared light travels in a banana-shaped arc from the emitting to the receiving diode. Most NIRS devices use spatial resolution by incorporating 2 receiving electrodes in a certain distance into their sensors, allowing to subtract signals coming from superficial (absorbance by skull and skin, detected by the shorter distance sensor) from those of deeper tissues (representing gray matter of the brain, assessed by the larger sensor distance), with a penetration depth of about 15 mm for the (larger) sensor distance of 40 mm. Another technique provides a tissue oxygen index (expressed in %) and concentration change in oxyhemoglobin by simultaneously integrating spatially resolved spectroscopy and the modified Beer-Lambert law. The spatially resolved spectroscopy technique is based on gathering the light signals at multiple closely spaced detectors. Because the depth of photon penetration is proportional to the source-detector distance, analyzing the differential signal as a function of this distance provides assessment of changes in oxygen saturation occurring in deep rather than superficial tissue layers.

It has to be noted that NIRS measures the hemoglobin oxygen saturation within the microvessels (diameter <100 µm) and not the intracellular oxygenation (as the term tissue oxygenation erroneously implies). When calculating ScO₂ values from absorption analysis, most devices assume a fixed ratio of the contribution of 20%–25% arterial and 75%–80% venous blood to the signal (neglecting the capillary blood volume of about 5%). This fixed ratio may however vary considerably between individuals, may be more influenced by arterial blood, and may depend on changes in body position (such as Trendelenburg or beach chair) or during hypoxia.

Due to variations in the sensor technology and algorithms used, absolute ScO₂ levels differ between various commercial devices and are not directly comparable. Based on data from volunteers undergoing tilting table maneuvers, as well as patients undergoing awake carotid endarterectomy, a decrease in relative ScO₂ levels to more than 20% of baseline has been associated with a reduction in CBF severe enough to be accompanied by a loss of consciousness. Thus, it has been argued that the interpretation of ScO₂ levels for most cerebral oximeters should not be based on absolute values rather than follow a trend analysis instead, ie, by interpreting the relative changes of ScO₂ in relation to individual baseline values (before an intervention).

However, there is also evidence that absolute levels of ScO₂ comprise clinically relevant information beyond cerebral oxygenation because pre- and perioperative ScO₂ levels below a certain cutoff level (usually 50%–60%) have been associated with an increase in neurological and/or general complications and increased mortality. As exemplified in the Figure, pronounced cerebral desaturations or bitemporal differences in ScO₂ might indicate inadequately perfused brain tissue at risk of cerebral infarction and initiate further postoperative diagnostics. Observational studies have shown associations between ScO₂ and a variety of demographic, anamnestic, and cardiovascular risk variables including age, body mass index, hematocrit, and left ventricular ejection fraction. Moreover, clinically relevant associations between humoral cardiopulmonary function markers like high-sensitive troponin T and the N-terminal prohormone of B-type natriuretic peptide have been observed in patients scheduled for cardiac surgery. These findings clearly support the notion that absolute levels of ScO₂ do indeed provide useful information, but also point to a clinically relevant influence of systemic factors (perfusion and oxygen balance) on ScO₂.

In line with this, the normal range of ScO₂ in healthy volunteers has been reported to be around 70% ± 6% (range,
58%–82%), while patients with cardiovascular disease scheduled for cardiac surgery frequently present with lower ScO2 baseline levels of about 65% ± 9% with a typical range between 47% and 83%. Assuming typical average values for oxygen saturation of the arterial blood of 97% and a SvO2 of 60.7% and an arterial to venous blood ratio of 25/75 contributing to the signal (see above), we can calculate a normal ScO2 level of about 69.8% (97% × 0.25 + 60.7% × 0.75), which is close to the values found in healthy volunteers. Given a standard deviation of 6%, this implies that ScO2 levels below 58% (69.8% – 1.96 × 6%) represent cerebral ischemia or hypoxia, while ScO2 levels above 81.5% (69.8% + 1.96 × 6%) in general indicates an adequate (frontal) cerebral perfusion. Of note, high ScO2 values can also indicate hyperperfusion (as seen with hypercapnia). Absolute ScO2 values between 58% and 81.5% thus represent the gray zone of inconclusive values, where its diagnostic ability is limited and should not lead to therapeutic interventions. Yet, this range will include most of the clinical measurements, and coincidentally represents the normal range of ScO2 in healthy volunteers (see above).

**Indications.** In contrast to the aforementioned technologies for brain oxygenation, after introduction in clinical practice, cerebral oximetry was predominantly used outside neuroanesthesia and neurocritical care in patients undergoing cardiovascular surgery with a high risk of compromised cerebral perfusion, ie, in cardiac and carotid surgery. However, within the last years, the use of cerebral oximetry has broadened and the technology is now increasingly used in other clinical settings like in high-risk noncardiac surgery, in patients undergoing anesthesia in the beach chair position (eg, for shoulder surgery), in patients with stroke undergoing thrombectomy, during extracorporeal life support and membrane oxygenation, in the intensive care unit and during cardiopulmonary resuscitation, just to name a few.

Despite these developments, scientific evidence on the effects of cerebral oximetry on clinical outcomes is controversial. The most recent systematic review—focusing on the prevention of neurological complications in cardiac surgical patients—neither found conclusive evidence that a decrease in cerebral oxygen saturation was associated with an increased rate of neurological complications (delirium/POCD/stroke) nor that a therapy aiming to avoid cerebral desaturation prevented any of these complications. In contrast, taking into account also systemic complications and including more recent findings from the cardiovascular field (Table 1) and studies on patients undergoing other types of surgery as well (Table 2), a completely different picture arises: not only that a majority of study results clearly supports that there is indeed an association between a perioperatively decreased ScO2 and an increased complication rate, but there is also a majority of studies showing that a goal-directed therapy aiming to avoid cerebral desaturations is effective in terms of a reduction in cerebral and/or systemic complications (Tables 1 and 2). The latter approach has been challenged by 2 recent multicenter trials (1 being primarily a feasibility study) and a systematic review that failed to show significant effects of interventions or algorithms to prevent or restore a perioperatively decreased ScO2.

Currently there are no formal guidelines on the use of cerebral oximetry in cardiovascular surgery available. However, there is consensus to use this technology in patients undergoing aortic arch surgery and in the pediatric cardiac surgical population, and maybe also in patients with history of hypertension, carotid stenosis, or cerebral ischemia.

**Limitations.** As stated above, the cerebral oximetry signal is influenced by a variety of variables reflecting systemic perfusion, probably due to the fact that the signal is—at least partially—“contaminated” by extracranial perfusion. For example, despite still a little bit controversial with respect to the confounding influence of cerebral autoregulation, some studies clearly show that the application of vasopressors affects NIRS-derived ScO2, whereas invasively derived cerebral oxygenation remains
<table>
<thead>
<tr>
<th>Medical Discipline: Cardiac Surgery</th>
<th>Study Type</th>
<th>Publication Year</th>
<th>No. of Patients</th>
<th>Principal Findings</th>
<th>Supporting an Association Between Low ScO₂ and Poor Outcomes</th>
<th>Supporting That Goal-Directed Optimization of ScO₂ Improves Outcomes</th>
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<tbody>
<tr>
<td>Reents et al95</td>
<td>Prospective observational</td>
<td>2002</td>
<td>47</td>
<td>No association between cerebral desaturation and cognitive decline</td>
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<td>Goldman et al134</td>
<td>Cohort study</td>
<td>2004</td>
<td>2279</td>
<td>Improved general and neurological outcomes after implementation of goal-directed optimization of ScO₂</td>
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<td>+</td>
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<td>Yao et al95</td>
<td>Prospective observational</td>
<td>2004</td>
<td>100</td>
<td>Cerebral desaturation is associated with cognitive decline</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Negargar et al135</td>
<td>Prospective observational</td>
<td>2007</td>
<td>72</td>
<td>No association between cerebral desaturation and cognitive decline</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Hong et al97</td>
<td>Prospective observational</td>
<td>2008</td>
<td>100</td>
<td>No association between cerebral desaturation and cognitive decline; any association between cerebral desaturation and prolonged hospital stay</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Slater et al136</td>
<td>RCT and post hoc observational</td>
<td>2009</td>
<td>265</td>
<td>No differences between interventional and control group (ScO₂ goals in the intervention group not met). Cerebral desaturation is associated with cognitive decline</td>
<td>+</td>
<td>+ (-)</td>
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<tr>
<td>Schön et al98</td>
<td>Retrospective matched pairs analysis</td>
<td>2009</td>
<td>800</td>
<td>Cerebral desaturation is associated with increased complications and prolonged hospital stay</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Murkin et al137</td>
<td>RCT</td>
<td>2009</td>
<td>200</td>
<td>Goal-directed optimization of ScO₂ leads to reduced morbidity</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Fischer et al138</td>
<td>Prospective observational</td>
<td>2011</td>
<td>30</td>
<td>Cerebral desaturation is associated with increased complications</td>
<td>+</td>
<td>-</td>
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<tr>
<td>De Tournay-Jette et al99</td>
<td>Prospective observational</td>
<td>2011</td>
<td>61</td>
<td>Cerebral desaturation is associated with cognitive decline</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Schoen et al140</td>
<td>RCT (comparison between cognitive effects of volatile and propofol-based anesthesias)</td>
<td>2011</td>
<td>128</td>
<td>Cerebral desaturation is associated with cognitive decline in patients undergoing propofol-based anesthesia</td>
<td>+</td>
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<tr>
<td>Schoen et al94</td>
<td>Prospective observational</td>
<td>2011</td>
<td>231</td>
<td>Low ScO₂ is an independent predictor of postoperative delirium. Increased incidence of delirium in patients with preoperatively normal ScO₂ and intraoperative desaturation</td>
<td>+</td>
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<tr>
<td>Heringlake et al92</td>
<td>Prospective observational</td>
<td>2011</td>
<td>1178</td>
<td>Preoperatively low ScO₂ is independently associated with morbidity and mortality</td>
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<tr>
<td>Palmberger et al145</td>
<td>Retrospective cohort study</td>
<td>2012</td>
<td>642</td>
<td>Implementation of goal-directed optimization of ScO₂ leads to reduced delirium and length of stay</td>
<td>+</td>
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<tr>
<td>Mohandas et al142</td>
<td>RCT</td>
<td>2013</td>
<td>100</td>
<td>Goal-directed optimization of ScO₂ leads to less cognitive decline and shorter PACU stay</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Colak et al143</td>
<td>RCT</td>
<td>2015</td>
<td>200</td>
<td>Goal-directed optimization of ScO₂ leads to less cognitive decline</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Sun et al143</td>
<td>Prospective observational</td>
<td>2014</td>
<td>2097</td>
<td>Preoperatively low ScO₂ is independently associated with morbidity and mortality</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Kok et al144</td>
<td>RCT</td>
<td>2014</td>
<td>60</td>
<td>No association between cerebral desaturation and cognitive decline</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Deschamps et al145</td>
<td>RCT</td>
<td>2016</td>
<td>200</td>
<td>Goal-directed optimization of ScO₂ did not lead to reduced morbidity</td>
<td>-</td>
<td>-</td>
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<td>Rogers et al146</td>
<td>RCT</td>
<td>2017</td>
<td>208</td>
<td>No effect on cognitive function of a personalized optimization of ScO₂</td>
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<tr>
<td>Lei et al147</td>
<td>RCT</td>
<td>2017</td>
<td>250</td>
<td>Restoration of low ScO₂ did not result in lower postoperative delirium rates</td>
<td>+</td>
<td>-</td>
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</table>

Relevant publications on the association between low or perioperatively decreased cerebral oxygen saturation and cerebral outcomes in cardiac surgery, showing that the overwhelming number of observational and randomized trials and cohort studies show a positive association between cerebral desaturation and an increased incidence of neurological and/or general complications. + indicates positive result and − indicates negative result.

Abbreviations: PACU, postanesthesia care unit; ScO₂, cerebral oxygen saturation; RCT, randomized controlled trial.
<table>
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<th>Medical Discipline</th>
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</thead>
<tbody>
<tr>
<td>Abdominal Surgery</td>
<td>RCT</td>
<td>2005</td>
<td>122</td>
<td>Goal-directed optimization of ScO₂ leads to less cognitive decline and shorter length of PACU and hospital stay</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Casati et al[148]</td>
<td>Prospective observational</td>
<td>2007</td>
<td>60</td>
<td>Cerebral desaturation is associated with prolonged hospital stay</td>
<td></td>
<td>+</td>
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<tr>
<td>Ballard et al[149]</td>
<td>Prospective cohort study and RCT</td>
<td>2012</td>
<td>411</td>
<td>Goal-directed optimization of ScO₂ leads to reduced cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Orthopedic Surgery</td>
<td>Prospective observational</td>
<td>2013</td>
<td>50</td>
<td>No association between cerebral desaturation and cognitive decline</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>Salazar et al[199]</td>
<td>Prospective observational</td>
<td>2013</td>
<td>46</td>
<td>Cerebral desaturation is associated with cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Ni et al[55]</td>
<td>Prospective observational</td>
<td>2015</td>
<td>78</td>
<td>Cerebral desaturation is associated with cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Trafidlo et al[150]</td>
<td>Retrospective cohort study</td>
<td>2015</td>
<td>43</td>
<td>Use of cerebral oximetry leads to less cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Kim et al[152]</td>
<td>Prospective observational</td>
<td>2016</td>
<td>87</td>
<td>Association between cerebral desaturation and cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Meng et al[153]</td>
<td>Prospective observational</td>
<td>2017</td>
<td>108</td>
<td>No association between cerebral desaturation, complications, and hospital length of stay</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>Lung Surgery</td>
<td>Prospective observational</td>
<td>2012</td>
<td>76</td>
<td>Association between cerebral desaturation and cognitive decline</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Intensive Care Unit</td>
<td>Prospective observational</td>
<td>2017</td>
<td>89</td>
<td>Association between cerebral desaturation and delirium</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Relevant publications on the association between low or perioperatively decreased cerebral oxygen saturation and cerebral outcomes in different surgical disciplines (excluding cardiac surgery), showing that the overwhelming number of observational and randomized trials and cohort studies show a positive association between cerebral desaturation and an increased incidence of neurological and/or general complications. + indicates positive result and - indicates negative result.

Abbreviations: PACU, postanesthesia care unit; ScO₂, cerebral oxygen saturation; RCT, randomized controlled trial.
unchanged. Moreover, extracranial contamination may—at least in part—explain the association between preoperative ScO2 and clinical outcomes in the cardiac surgical population, as well as the correlation of ScO2 with mixed venous oxygen saturation. Moreover, extracranial contamination of global brain oxygen balance by SjvO2. The latter refers to the fact that—as described above—all cerebral oximeters are calibrated assuming a fixed ratio between arterial and venous blood in the brain, based on the direct measurements of arterial and venous saturations. Consequently, all limitations ascribed to the precision of SjvO2—measurements apply also to the calibration process of these devices; and besides sensor technology and wavelengths used, this may explain some of the variability observed between available cerebral oximeters from different manufacturers.

Comparability of Brain Oxygenation Measurements With Different Technologies. As discussed above, only few technologies for monitoring oxygen in the brain in the clinical setting are available, and—despite technical advancements—we are still far from having a clinical gold standard to universally accomplish this goal. And it remains highly questionable if such a “gold standard” will be developed within the foreseeable future.

Taking into account the clinically available technologies, the spectrum reaches from highly invasive probes monitoring oxygen tension in an extremely small area of brain tissue (not discussed within this review article) to the truly noninvasive technology of NIRS—within the limitation of being influenced by extracranial contamination, but being capable of interrogation of a broader area of vulnerable brain tissue further to the evaluation of global brain oxygen balance by SjvO2. The latter again being influenced by anatomic factors difficult to estimate and, comparably to NIRS-derived oxygenation, by systemic perfusion. Consequently, it is not astonishing that comparison studies failed to show comparability between the different monitoring modalities.

However, from a clinical point of view, if no gold standard is available, it seems reasonable—if any—to choose the monitoring modality for which improvements in outcomes have most consistently been demonstrated. At present, this does only apply to the use of cerebral oximetry in patients undergoing cardiac surgery.

Autoregulation of CBF
Autoregulation of blood flow is a key feature of the human cerebral vasculature to guarantee adequate oxygenation of the brain under changing physiological conditions. This is essential because, due to its high metabolic activity, the brain does not tolerate hypoxia or hypoperfusion. The autoregulation of CBF provides a steady flow of blood toward the brain by altering vascular resistance through complex myogenic, neurogenic, and metabolic mechanisms. This autoregulatory control mechanism therefore buffers any variations in MAP and CPP and is effective in a MAP range between approximately 50 and 150 mm Hg, defining the lower limit of autoregulation (LLA) and upper limit of autoregulation, respectively. This range of intact autoregulation may, however, vary considerably between individuals, and shifts to higher thresholds have been observed in elderly and hypertensive patients. At the blood pressure extremes, ie, below the LLA and above the upper limit of autoregulation, the cerebral vasculature is no longer able to adapt its resistance in response to further blood pressure changes. The clinical consequence is that, for instance, intraoperative hypotension (ie, MAP values below the LLA) will be poorly tolerated, and might cause ischemic events and postoperative neurological complications, as well as dysfunction of other pressure-dependent organs like the kidneys. Interestingly, recent evidence from observational trials is clearly supporting this concept.

Assuming that ScO2 is a reliable surrogate of CBF, it has been shown that—based on continuous correlation analyses between ScO2 and MAP and calculation of a cerebral oximetry index—the individual LLA can be determined at the bedside and in the operating room and that perfusion below the LLA is associated with postoperative morbidity as well as increased expression of a biomarker of neurological damage. Furthermore, assessment of cerebral autoregulation has been used to explain paradoxical changes in ScO2 induced by vasoactive medication, which was found exclusively in patients with intact cerebral autoregulation.

A recent meta-analysis including 33 studies and 3059 patients confirmed that cerebral autoregulation monitoring could predict mortality in patients with traumatic brain injury and with subarachnoid hemorrhage, and that continuous assessment of cerebral autoregulation predicted outcome better than intermittent monitoring.

CONCLUSIONS
There is increasing evidence that the use of brain function monitoring by processed EEG and brain oxygenation monitoring by NIRS are useful adjuncts for improving patient care in the perioperative period.

EEG-derived parameters may be especially helpful for optimizing anesthetic titration to avoid unwarranted effects of inappropriately deep anesthesia and promoting fast postoperative recovery.

The invasive technologies of direct brain tissue oxygen monitoring and jugular venous oxygen saturation monitoring—despite of debatable reliability—may be helpful in selected patients undergoing anesthesia and intensive care treatment for neurological disorders, but hardly play a role outside neurocritical care.

In contrast, increasing evidence suggests that avoiding a mismatch between brain oxygen delivery and demand by goal-directed optimization of NIRS-derived cerebral oxygen saturation leads to a reduction of neurological and/or general perioperative complications. Recent evidence points out that this technology may be additionally used to assess autoregulation of CBF and thereby help to titrate arterial blood pressure to the individual needs and for bedside diagnosis of disturbed autoregulation.

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**Contribution:** This author helped write and edit the manuscript.

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### REFERENCES

1. Patel D, Lunn AD, Smith AD, Lehmann DJ, Dorrington MN, Orion Pharma (Espoo, Finland), Amomed Pharma (Vienna, Austria), Tenax Therapeutics (Morrisville, NC), Fresenius Medical (Bad Homburg, Germany), and Baxter Medical (Unterschleissheim, Germany).

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This manuscript was handled by: Maxime Cannesson, MD, PhD.

### REFERENCES


34. Chiu CL, Ong G, Majid AA. Impact of bispectral index monitoring on propofol administration in patients...


