



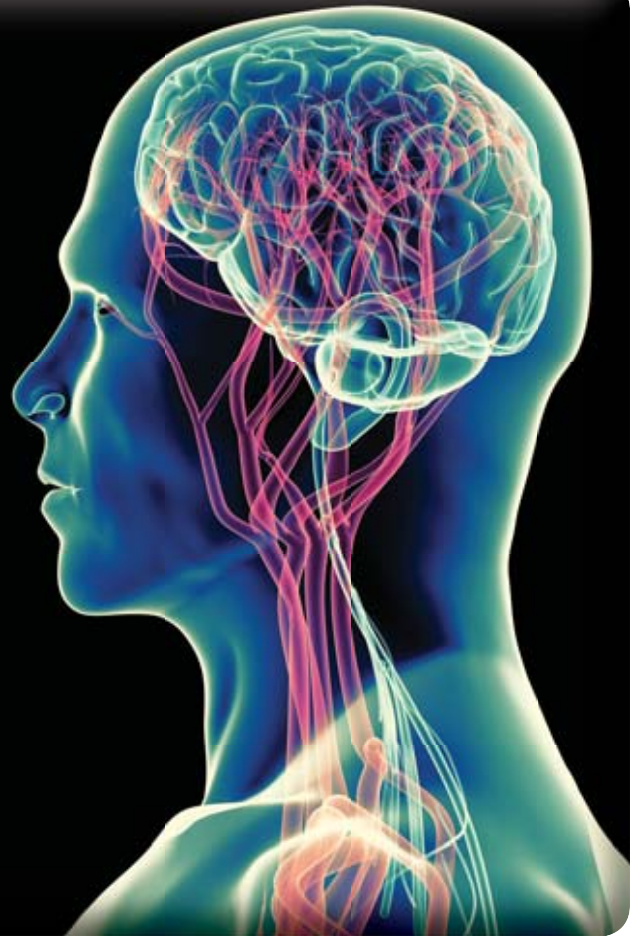
Cerebral Oximetry

Emerging Applications For an Established Technology

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Cerebral oximetry has been studied for more than 30 years, and has been commercially available to clinicians for more than 2 decades.^{1,2} However, whereas pulse oximetry has been a standard of care for decades, only recently has cerebral oximetry been extensively studied and adapted to investigate changes in oxygen delivery to the brain and how the monitor may be used as a “first alert” of impending organ dysfunction.³

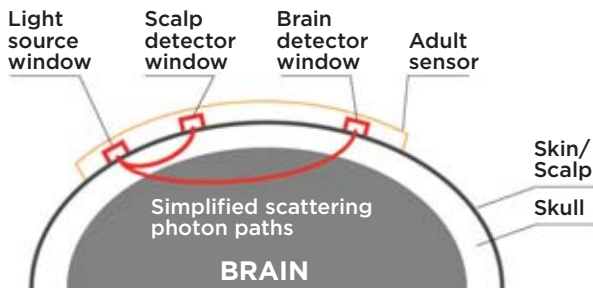
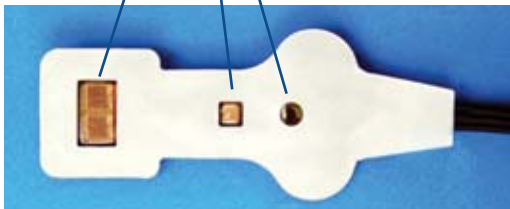
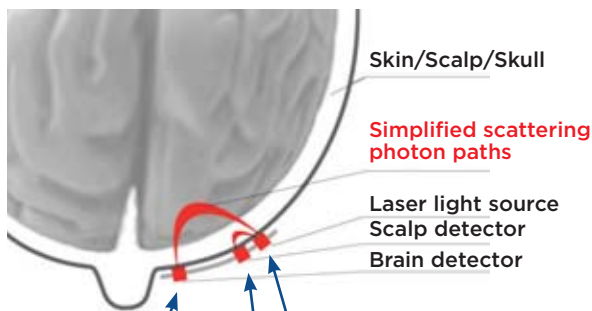
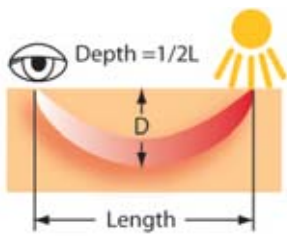


Figure 1. The technology of cerebral oximetry allows sampling of tissue from 2 photodetectors, each with light sources penetrating to different depths to determine tissue oxygenation.

Courtesy of G. Fischer, MD

Cerebral oximetry estimates the oxygenation of regional tissue by transcutaneous measurement of the cerebral cortex, an area of the brain that is particularly susceptible to changes in the demand and supply of oxygen, and which has a limited oxygen reserve. Measurement is based on the ability of light to penetrate the skull and to determine hemoglobin oxygenation according to the amount of light absorbed by hemoglobin—a process called near-infrared spectroscopy (NIRS).⁴ Unlike pulse oximetry (which uses a single sensor), cerebral oximetry with NIRS uses 2 photodetectors with each light source. The technology allows selective sampling of tissue beyond a specified depth beneath the skin (Figure 1). Near-field photodetection then can be subtracted from far-field detection to provide selective measurements of tissue oxygenation. Adhesive pads applied over the frontal lobes both emit and capture reflected near-infrared light passing through the cranial bone to and from the underlying cerebral tissue.

Tissue sampling by cerebral oximetry is mainly from venous (70%-75%) rather than arterial (25%) blood and is independent of pulsatile flow (Figure 2). Monitoring is noninvasive and can provide an early warning of decreased oxygen delivery. Many cardiothoracic and vascular anesthesiologists have adopted the technique to provide continuous intraoperative insight into brain perfusion and oxygenation dynamics.

The FDA has approved 4 cerebral oximeters: the CerOx (Ornim; Figure 3) Equanox (Nonin; Figure 4), Fore-Sight (CASMED; Figure 5), INVOS (Covidien; Figure 6). Normal cerebral oxygen saturation (rSO_2) values are available for each manufacturer's device; for example, the INVOS 5100 specifies a normal value for an adult cardiac surgery patient of 67% ($\pm 9\%$). Baseline rSO_2 values for bilateral room air should be established before the induction of general anesthesia or measurement by secure adherence of the pads to the skin. Values must be interpreted in the context of available clinical information because many factors alter measurements. These factors include cardiac output, blood pressure, hypo/hypercapnia, arterial pH, inspired oxygen concentration, temperature, local blood flow, hemoglobin (Hb) concentration, hemorrhage, embolism, preexisting disease (particularly cerebral infarction), and change of position.

With so many variables, there is no gold standard test to unequivocally validate that cerebral oximetry reflects regional oxygenation of frontal lobe tissue. Also, given that the technology of the several devices differs, individual validation is required. It may be reasonable to infer that invasive and direct measurement of regional tissue oxygen pressure ($tiPO_2$) might be equivalent to rSO_2 , but these are not the same parameters even if some correlations may exist.

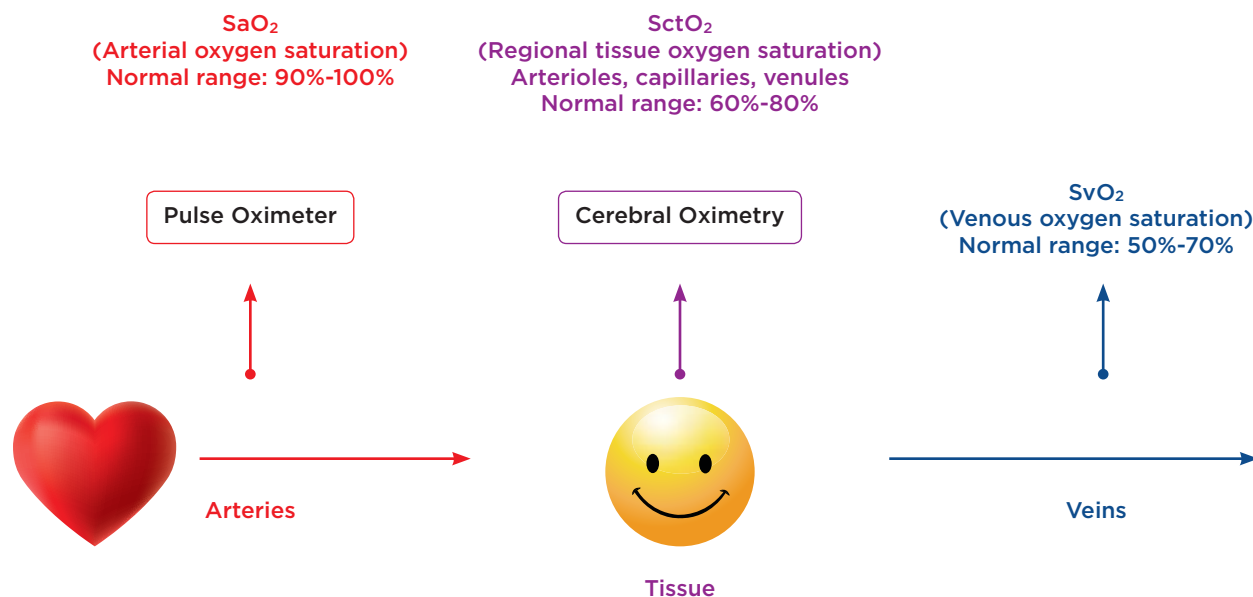


Figure 2. Tissue sampling by cerebral oximetry is derived from both venous and arterial blood and thus values fall between the 2.

Courtesy of G. Fischer, MD

The adequacy of global oxygen delivery also depends on central venous saturation. Traditional techniques required the placement of invasive devices for central venous access. A recent study of 40 patients compared 2 noninvasive technologies for the estimation of regional venous saturation (reflectance plethysmography and NIRS), using analysis of venous blood gas as the standard.⁵ In the first group, a reflectance pulse oximeter probe was placed on the skin overlying the internal jugular vein. In the second group, a cerebral oximeter patch was placed on the skin overlying the internal jugular vein as well as the ipsilateral cerebral hemisphere.

Oxygen saturation estimates from both groups were compared with measured saturation from venous blood. Correlation was statistically significant for NIRS, but not for transcutaneous regional oximetry. Placement of cerebral oximetry patches directly over the internal jugular vein (as opposed to on the forehead) appeared better to approximate internal jugular venous saturation, suggesting this modality may offer clinically useful information regarding global cerebral oxygen supply and demand matching. These findings were confirmed by Marimon et al in a study of 20 pediatric patients undergoing cardiac surgery.⁶ Cerebral oximetry and somatic renal oxygen saturation correlated significantly with continuous oxygen saturation from a central venous catheter.

The 'Index' Organ

In addition to providing continuous insight into regional oxygenation of the brain, cerebral oximetry may allow clinicians to use the brain as an index organ that points to the adequacy of tissue perfusion and oxygenation of other vital organs. This concept has received support from multiple clinical outcome studies.^{3,7,8}

Data from the Society of Thoracic Surgeons (STS) National Database strongly suggest that the intraoperative use of cerebral oximetry in cardiac surgery patients frequently (23%) served as a "first-alert" indicator of an intraoperative dynamic that could lead to potential adverse clinical outcomes in both adult and pediatric patients. The STS has the world's largest database of cardiothoracic cases, with more than 500 participating centers contributing procedural data for in excess of 3.77 million. The database now includes 7 fields related to cerebral oximetry (Table 1). Fields 1 and 2 collect right and left baseline rSO₂ values before the induction of anesthesia; 3 and 4 relate to both left and right cumulative saturation values below the threshold (25% below baseline). The cumulative values are captured as the area under the curve (AUC), and include both the time spent below the lower threshold as well as the magnitude of these excursions. Thus, the units of AUC are minute • %. For example, if a patient



Figure 3. CerOx (Ornim).

had a unilateral (left-sided) oxygen desaturation of 15% below the critical lower threshold for a total of 10 minutes for the entire surgical procedure, the left-sided AUC value would be 150 minutes • %. Fields 5 and 6 record rSO₂ values at skin closure. Field 7 asks if the use of rSO₂ monitoring during the procedure was a sentinel indicator of an intraoperative event that might have led to an adverse outcome. Taken together, these data fields will provide important insight into the clinical utility of rSO₂ monitoring.

The Duke Clinical Research Institute examined the STS Adult Cardiac Surgery Database cerebral oximetry parameters collected from January 2008 to December 2009, specifically looking at whether item 7 was a first alert.³ This ongoing analysis established that in 23% of procedures (8,406 of 36,548), cerebral oximetry provided the first indication of impending potential clinical problems.

Several large clinical trials of cerebral oximetry have been conducted. In a retrospective study of 2,279 cardiac surgery patients, Goldman et al assessed 2 groups of patients, 1 of which received rSO₂ monitoring.⁹ Significant reduction of stroke (0.97% rSO₂ group vs 2.5% controls; $P < 0.044$), duration of mechanical ventilation after surgery (6.8% rSO₂ vs 10.6% controls; $P < 0.0014$), and hospital length of stay ($P < 0.046$) were established in the monitored group. The most notable differences in outcomes were found among the patients rated New York Heart Association Class I, indicating that the benefits of monitoring not only extend to the sickest individuals.

Prospective, randomized controlled trials examining the effects of employing rSO₂ monitoring in cardiac surgery patients also have been conducted. Murkin et al



Figure 4. Equanox (Nonin).

examined the results for patients in whom saturations fell below 75% of preoperative levels and were treated, and compared the outcomes with those for untreated patients.⁷ Untreated patients spent more time in the intensive care unit than those in the active treatment group ($P = 0.029$), and had significantly greater morbidity and mortality ($P = 0.048$).

Preoperative phlebotomy has been used to minimize the need for allogenic blood products, especially in cardiac surgery. Removed blood is replaced with IV fluids. Such normovolemic hemodilution may present problems during cardiopulmonary bypass when further hemodilution may result in very low Hb levels. Dewhirts and colleagues found that volume replacement was better guided by rSO₂ than by hemodynamic variables in 38 patients (aged 3 months to 50 years; *Pediatr Cardiol.* 2012 Jun 1 [Epub ahead of print]).

Another recent study sought to predict the limits of cerebral autoregulation during cardiopulmonary bypass.¹⁰ Patients undergoing this procedure exhibit a wide range of mean arterial pressures at the lower limit of autoregulation, making standard blood pressure an unreliable means of estimating or determining this important target. Joshi et al used real-time monitoring of rSO₂ on 232 patients and found that it provided more accurate information than routine blood pressure monitoring in identifying the lower limit of autoregulation. The lower limit of autoregulation could be identified with cerebral oximetry in 219 patients. Preoperative systolic blood pressure was associated with a higher lower limit of autoregulation, but only for patients whose



Figure 5. Fore-Sight (CASMED).

systolic blood pressure was 160 mm Hg or less.

Pedrini et al assessed the reliability of cerebral oximetry during carotid endarterectomy under general anesthesia.¹¹ Their study of 473 patients (mean age, 73 years) used a cutoff of 25% or 20% below baseline for prolonged hypoperfusion. Three patients presented with transient ischemic deficits at awakening, but no cases of death or stroke were observed. Shunting was required in 41 patients; in 30 the decision was made based on initial rSO_2 and in 11 after an intraoperative decrease of rSO_2 . Using the AUC analysis, for a greater than 25% reduction from baseline, sensitivity was 100% and specificity was 91%.

Stilo and colleagues enrolled 100 consecutive patients scheduled to undergo carotid endarterectomy and monitored bilateral rSO_2 . They considered a drop of greater than 20% to indicate cerebral ischemia. Nine patients showed a significant drop in rSO_2 ; 5 were shunted and 6 showed no change in consciousness. The authors suggested that the usefulness of cerebral oximetry in predicting cerebral ischemia was modest but monitoring with the INVOS 4100 had a high negative but low positive predictive value (*Minerva Anesthesiol.* 2012 Aug 3 [Epub ahead of print]).

Other studies in general surgery and geriatric patients have found similar improvement when rSO_2 values that fall below 75% of baseline are aggressively treated.⁸ Control patients experiencing cerebral desaturation intraoperatively had significantly longer stays in the postanesthesia care unit and lower scores on the Mini-Mental Status Examination at postoperative



Figure 6. INVOS (Covidien).

day 7 ($P=0.02$) than did patients treated for desaturation. A study by Tang et al of 76 patients undergoing thoracic surgery with single-lung ventilation found that early cognitive dysfunction was directly related to an intraoperative decline of rSO_2 .¹² In fact, more than 600 peer-reviewed retrospective studies, prospective observational studies, and case reports attest to the clinical value of rSO_2 monitoring in critical care and operative settings.³

A warning has been raised concerning the effects of lung recruitment maneuvers on cerebral oxygenation. Although an increase in intrathoracic pressure to 40cm H₂O for 20 seconds (commonly done after cardiac surgery) increases paO_2 significantly, mean arterial pressure also is decreased. This change is reflected in a significant decrease in rSO_2 . Thus, arterial pressure should be kept within the limits of cerebral autoregulation.¹³

Beyond the Surgical Patient

Although rSO_2 monitoring occurs mainly in the operating room, a 2009 study by Padmanabhan et al evaluated the utility of the technology for patients in the emergency room.¹⁴ They found poor correlation between NIRS cerebral oximetry, pulse oximetry, and capnography among 100 children aged 9 months to 18 years. Various agents were used including ketamine, fentanyl, dexmedetomidine (Precedex, Hospira), and propofol. Changes in rSO_2 occurred in 2.1% of patients and were associated with changes in SpO_2 23% of the time and changes in end-tidal CO_2 29% of the time, making it a more sensitive indicator of problems developing. Few hypoxic events resulted in changes in rSO_2 , but these episodes were not accompanied by changes in cardiorespiratory parameters. However, most of the children were otherwise healthy and deemed suitable candidates for off-site sedation. Thus, rSO_2 appears to

Table 1. The Society of Thoracic Surgeons National Database Fields Related to Cerebral Oximetry

Pre-induction baseline regional oxygen
 Saturation: Left: _____ (%) Right _____ (%)

Cumulative saturation below threshold:
 Left: _____ (minute %) Right _____ (minute %)

Skin closure regional oxygen saturation:
 Left: _____ (%) Right _____ (%)

Cerebral oximeter provided the first indication:
 Yes No

be a more sensitive measure of cerebral oxygenation than pulse oximetry, but isolated decreases in rSO₂ in children may not correlate well with short- or long-term neurologic complications. More studies in this area clearly are necessary.

Other studies in children have compared tissue oximetry in somatic sites with that of the cerebral cortex. Mittnacht summarized recent developments and available data on the use of NIRS in children at risk for low perfusion, postulating that during states of low cardiac output, cerebral blood flow, and thus cerebral NIRS, may be better preserved than in somatic tissue sites.¹⁵ Similarly, Kreeger et al evaluated cerebral oximetry in 100 children with congenital cardiac disease and found that it accurately measured the absolute value of cerebral saturation over a wide range of oxygenation and subject characteristics, offering considerable advantages.¹⁶

Sites other than the frontal cerebral cortex—such as the abdomen, flank, and muscle—have been investigated for a possible correlation with invasive measures of systemic perfusion and oxygenation. The abdomen seems preferable to the flank; therefore, to increase the sensitivity, specificity, and positive predictive value of tissue oximetry to detect systemic hypoperfusion, multisite NIRS, such as a combination of cerebral and somatic sites, has been proposed. NIRS also has been used to assess systemic perfusion in patients undergoing first-stage palliation for hypoplastic left heart syndrome.¹⁵ Multisite measuring is in the early stages. NIRS has been shown to predict low cardiac output, with decreases in rSO₂ serving as an early warning of problems developing in other organ systems.

Yet another innovative application is in children with sickle cell disease. Quinn and Dowling showed in 149

children (112 HbSS; 37 HbSC) that cerebral desaturation, a physiologic marker of the at-risk brain, could be detected by cerebral oximetry. The authors found that rSO₂ correlated with age, sex, Hb concentration, reticulocytes, HbF, and SpO₂, but not with blood flow velocities measured by transcranial Doppler. They stated that the monitor had the potential to improve identification of children at risk (especially those with HbSS) and to serve as a physiologic guide for neuroprotective therapy such as transfusion.¹⁷

Very low-weight neonates (<30 weeks and <1,500 g) usually are subjected to blood pressure monitoring, and based on findings of hypotension (<30 mm Hg) are treated with boluses of fluid and/or dopamine. Although these 2 therapies did increase blood pressure in one study of 28 patients, they did not affect cerebral saturation—suggesting that they are of minimal value, as the babies are most likely in an autoregulatory zone for cerebral blood flow.¹⁸

In the field of trauma, cerebral oximetry also may have found a place. Taussky et al compared NIRS cerebral oximetry with computed tomography (CT) perfusion in 8 patients with brain injuries.¹⁹ The investigators found that mean cerebral blood flow measured by CT perfusion was 61 mL/100 g per minute for the left side and 60 mL/100 g per minute for the right. Mean NIRS values were 75 on the right and 74 on the left. Linear regression analysis demonstrated a statistically significant probability value (*P*<0.0001) for cerebral blood flow when comparing NIRS frontal oximetry with CT perfusion. Other investigators have used cerebral oximetry as an additional monitor in trauma patients at the scene and during transport of 33 ambulances and 32 helicopters.²⁰ For outdoor monitoring, adequacy of signal was approximately 50%, improving to 100% during road transport and 86% during helicopter transport. The investigators stated that not only was cerebral oximetry possible in this setting, but that it provided clinically valuable information.

Other in vitro trauma studies (in pigs) have determined that rSO₂ provides reproducible decreases during hemorrhage, and in time course to invasively measured cardiac output, but delayed by 3 to 9 minutes when compared with arterial blood and pulse pressures.²¹ Thus, rSO₂ may provide early warning of worsening hemorrhage when continuous blood pressure is not available.

Cerebral oximetry also may be a useful technique for predicting mortality from cardiac arrest. Nasir et al evaluated the role of cerebral oximetry in predicting the return of spontaneous circulation in 19 patients who experienced cardiac arrest in the hospital.²² Those with return of circulation had an rSO₂ greater than 30% for more than 50% of the time of resuscitation, whereas those who died had rSO₂ values less than 30% for more

Table 2. Why Cerebral Oximetry?

The brain:
Complex and fragile system
Typically demands ~15% of normal cardiac output
Consumes ~20% of all oxygen used by the body
Elapsed time critical in desaturation events
The need is critical:
Cerebral ischemia the leading cause of compromised neurocognitive outcomes
Brain function directly affected by duration of reduced oxygenation

than 50% of the time. Survivors also had a significantly greater change in rSO₂ from baseline than did nonsurvivors (310% vs 150%, respectively; $P < 0.05$). Table 2 summarizes how the use of cerebral oximetry represents a critical monitor of cerebral—and indeed, whole body—dysfunction.

Other studies have considered the value of rSO₂ in heart failure patients and found it to be a potential important biomarker and useful monitor of target organ perfusion.²³ Extracorporeal membrane oxygenation (ECMO) has been used in many critical situations, often for days. Although vital signs may be preserved, the question of whether brain perfusion is adequate has remained undetermined. Wong et al analyzed 20 patients for drops in rSO₂ to below 40 or greater than 25% of baseline.²⁴ Sensors were placed on the forehead and on the lower limbs. In all patients, rSO₂ dropped and therapy (fluids, increase in flow, vasopressors) was initiated, proving successful in 80% of patients. However, 4 patients were found to have suffered a stroke. In 6 patients, lower limb ischemia was detected and corrected with placement of a functioning distal perfusion catheter. The authors concluded that rSO₂ monitoring is important whenever ECMO is used to allow for correction of underlying ischemic processes and prevention of permanent ischemic damage.

Conclusion

Evidence suggests that the brain may act as an index organ for how well the vital organs are perfused and oxygenated. Cerebral oximetry has the potential to

provide a measurable clinical benefit beyond cardiovascular and thoracic procedures in ever-expanding situations. An aging population with decreasing organ function represents an increasing part of anesthesia practice. The use of cerebral oximetry, although not yet the standard of care, also might be useful in medicolegal situations. For example, a documented decrease in rSO₂ that prompted the insertion of a shunt would indicate that a subsequent neurologic deficit was probably not related to anesthetic care. This underused technology offers anesthesiologists a noninvasive tool to continuously monitor the oxygenation of cerebral tissue in virtually any general surgical patient treated either in and out of the hospital.

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