Appendix 1

Contributors: Perioperative Quality Initiative (POQI) 6 Workgroup participants

POQI chairs
Matthew D. McEvoy, MD
Department of Anesthesiology, Vanderbilt University Medical Center
Nashville, TN, USA

Timothy E. Miller, MD
Department of Anesthesiology, Duke University Medical Center
Durham, NC, USA

Tong Joo Gan, MD, MHS, FRCA, MBA
Department of Anesthesiology, Stony Brook University
Stony Brook, NY

Postoperative Delirium Workgroup
Christopher G. Hughes, MD, MS
Department of Anesthesiology, Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center and the Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN

Christina S. Boncyk, MD
Department of Anesthesiology, Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Vanderbilt University Medical Center; Nashville, TN, USA

Deborah J. Culley, MD
Department of Anesthesiology, Perioperative and Pain Medicine; Harvard Medical School, Boston, MA

Lee A. Fleisher, MD
Department of Anesthesiology and Critical Care, Penn Center for Perioperative Outcomes Research and Transformation, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Jacqueline M. Leung, MD, MPH
Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, CA

David L. McDonagh, MD
Departments of Anesthesiology and Pain Management, Neurological Surgery, and Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center
Dallas, TX

Electroencephalogram Workgroup
Matthew T.V. Chan, MB, BS, PhD, FHKCA, FANZCA, FHKAM
Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong
Hong Kong Special Administrative Region, China

Traci L. Hedrick, MD, MS

Department of Surgery, University of Virginia Health System
Charlottesville, VA

Talmage D. Egan, MD
Department of Anesthesiology, University of Utah School of Medicine,
Salt Lake City, UT

Paul Garcia, MD, PhD
Department of Anesthesiology, Columbia University
New York, NY

Susanne Koch, MD
Department of Anaesthesiology and Intensive Care Medicine, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin
Berlin, Germany

Patrick L. Purdon, PhD
Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, and Department of Anesthesia, Harvard Medical School
Boston, MA

Michael A. Ramsay, MD, FRCA
Department of Anesthesiology and Pain Management, Baylor University Medical Center
Dallas, TX

Spectroscopy Workgroup

Robert H. Thiele, MD
Departments of Anesthesiology and Biomedical Engineering; Divisions of Cardiac, Thoracic, and Critical Care Anesthesiology, University of Virginia School of Medicine
Charlottesville, VA

Andrew Shaw, MB FRCA FFICM FCCM MMHC
Department of Anesthesiology and Pain Medicine, University of Alberta
Edmonton, Alberta, Canada

Karsten Bartels, MD, PhD
Department of Anesthesiology, University of Colorado
Aurora, CO

Charles Brown, MD
Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University
Baltimore, MD

Hilary Grocott, MD, FRCPC, FASE
Department of Anesthesiology, Perioperative and Pain Medicine, University of Manitoba
Winnipeg, Manitoba, Canada

Matthias Heringlake
Department of Anesthesiology and Intensive Care Medicine, University of Lübeck, Germany
Lübeck, Germany

Appendix 2: Search Terms

Searches done without an informatician

1. What physiologic information can NIRS provide? (This question combines queries about what NIRS actually measures as well as whether or not it can identify the lower limit of auto regulation [LLA] for brain perfusion?)

Search "near infrared spectroscopy" and "physiology" and "brain" (Filters: Review)
Results: 203
Screened: 203
Downloaded (4):

Search "near infrared spectroscopy" and "jugular venous" and "oxygen"
Results: 79
Screened: 79
Downloaded (10):

Search for "near infrared spectroscopy" and "LiCOX"
Results: 5
Screened: 5
Downloaded: 2

Search for "spectroscopy, near-infrared" AND "arterial pressure"
Results: 214
Screened: 214
Downloaded: 15 - Done

Search "spectroscopy, near-infrared" AND "brain" AND "blood flow velocity"
Results: 118
Screened: 118
Downloaded: 4

Search "spectroscopy, near-infrared" AND "brain" AND "methods" AND "standards"
Results: 44
Screened: 44
Downloaded: 0

Search "spectroscopy, near-infrared" AND "Neurophysiological Monitoring"
Results: 27
Screened: 27
Downloaded: 0

2. Do technical aspects of NIRS devices (the algorithm, optode spacing, wavelength selection) used to derive the StO2 number matter?

Search "near infrared spectroscopy" and "optode spacing"
Results: 6
Screened: 6
Downloaded (0):

Search "oximetry" and "optode spacing"
Results: 3
Screened: 3
Downloaded (1):

Search "near infrared spectroscopy" and "wavelength selection"
Results: 73
Screened: 73
Downloaded (3):

3. During which components of the peri-operative period can NIRS be useful? (Pre-operative baseline helpful? Intraoperative, during cardiopulmonary bypass, post-operatively, both?)

Search "near infrared spectroscopy" and "preoperative" and "baseline"
Results: 36
Screened: 36
Download: 7

Search "near infrared spectroscopy" and "postoperative" and "baseline"
Results: 88
Screened: 88
Download: 2

Search "near infrared spectroscopy" and "postoperative" and "intensive care unit"
Results: 52
Screened: 52
Download: 6

4. Can using a NIRS-guided interventional algorithm reduce perioperative complications after [cardiac/high-risk non-cardiac] surgery?

Search "near infrared spectroscopy" and "surgery" and "stroke" and "acute kidney injury"
Results: 2
Screened: 2
Download: 0

Search "near infrared spectroscopy" and "surgery" and "stroke" (Filters: Clinical Trial)
Results: 11
Screened: 11
Download: 1

Search "cerebral oxygenation" and "surgery" and "stroke" (Filters: Clinical Trial)
Results: 9
Screened: 9
Download: 0

Search "cerebral oxygenation" and "surgery" and "acute kidney injury" (Filters: Clinical Trial)
Results: 1
Screened: 1
Download: 0

Search "near infrared spectroscopy" and "surgery" and "acute kidney injury" (Filters: Clinical Trial)
Results: 2
Screened: 2
Download: 0

Search "near infrared spectroscopy" and "randomized" and "surgery" (Filters: Clinical Trial)
Results: 94
Screened: 94
Download: 2

Searches done with an informatician

Search A (focused on Question 1)
Results 204
Screen 204
Downloaded 5

(near infrared spectroscop*[ti] OR near infrared spectromet*[ti] OR NIRS[ti] OR cNIRS[ti] OR NIR spectroscop*[ti] OR "Spectroscopy, Near-Infrared"[Majr])
AND (neuromonitor*[tiab] OR head[tiab] or crania*[tiab] or craniocerebral[tiab] or capitis[tiab] or craniu*[tiab] or cerebra*[tiab] or cerebru*[tiab] or brain*[tiab] or forebrain*[tiab] or skull*[tiab] or hemispher*[tiab] or intracran*[tiab] or encephal*[tiab])
AND
(physiolog*[ti] OR perfusion[ti] OR autoregulat*[ti] OR "cerebral blood flow"[ti] OR "mixed venous"[ti])

Search B (focused on Question 2)
Results 86
Screen 86
Downloaded 5

near infrared spectroscop*[ti] OR near infrared spectromet*[ti] OR NIRS[ti] OR cNIRS[ti] OR NIR spectroscop*[ti] OR "Spectroscopy, Near-Infrared"[Majr]) AND (neuromonitor*[tiab] OR head[tiab] or crania*[tiab] or craniocerebral[tiab] or capitis[tiab] or craniu*[tiab] or cerebra*[tiab] or cerebru*[tiab] or brain*[tiab] or forebrain*[tiab] or skull*[tiab] or hemispher*[tiab] or intracran*[tiab] or encephal*[tiab]) AND (optode*[tiab] OR wavelength[tiab] OR Invos*[tiab] OR "Covidien"[tiab] OR "Masimo"[tiab] OR "channels"[tiab])

Search C (focused on questions 3 and 4)
Results 56
Screen 56
Downloaded 11

(near infrared spectroscop*[ti] OR near infrared spectromet*[ti] OR NIRS[ti] OR cNIRS[ti] OR NIR spectroscop*[ti] OR "Spectroscopy, Near-Infrared"[Majr])
AND
(neuromonitor*[tiab] OR head[tiab] or crania*[tiab] or craniocerebral[tiab] or capitis[tiab] or craniu*[tiab] or cerebra*[tiab] or cerebru*[tiab] or brain*[tiab] or forebrain*[tiab] or skull*[tiab] or hemispher*[tiab] or intracran*[tiab] or encephal*[tiab])

AND
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])

Search D (focused on questions 3 and 4)
Results 25
Screen 25
Downloaded 9

(near infrared spectroscop*[ti] OR near infrared spectromet*[ti] OR NIRS[ti] OR cNIRS[ti] OR NIR spectroscop*[ti] OR "Spectroscopy, Near-Infrared"[Majr])
AND
(operati*[tiab] or perioperat*[tiab] or peroperat*[tiab] or preoperati*[tiab] or postoperat*[tiab] or intraoperat*[tiab] or surg*[tiab] OR "Perioperative Period"[Mesh] OR "Perioperative Care"[Mesh])
AND
("Cardiac Surgical Procedures"[Majr] OR cardiac*[tiab] OR heart[tiab] OR "Cardiopulmonary Bypass"[Mesh] OR “cardiopulmonary bypass”[tiab])
AND
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])

Search E (focused on questions 3 and 4)
Results 107
Screen 107
Downloaded 14

(near infrared spectroscop*[tiab] OR near infrared spectromet*[tiab] OR NIRS[tiab] OR cNIRS[tiab] OR NIR spectroscop*[tiab] OR "Spectroscopy, Near-Infrared"[Majr])
AND
(neuromonitor*[tiab] OR head[tiab] or crania*[tiab] or craniocerebral[tiab] or capitis[tiab] or craniu*[tiab] or cerebra*[tiab] or cerebru*[tiab] or brain*[tiab] or forebrain*[tiab] or skull*[tiab] or hemispher*[tiab] or intracran*[tiab] or encephal*[tiab])
AND
(operati*[tiab] or perioperat*[tiab] or peroperat*[tiab] or preoperati*[tiab] or postoperat*[tiab] or intraoperat*[tiab] or surg*[tiab] OR "Perioperative Period"[Mesh] OR "Perioperative Care"[Mesh])
AND
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])

Appendix 3: Detailed Description of Near-Infrared Spectroscopy (NIRS) Devices

The complexity of cerebral blood flow as well as the devices designed to measure ScO_2 require a working knowledge of both brain physiology and the scientific principles of NIRS in order to use cerebral oximetry effectively. Blood flow to the brain is a function of driving pressure and resistance, in accordance with the Hagen-Poiseulle law.[1,2] Because of its importance, the human brain has developed the ability to autoregulate blood flow within the "cerebral autoregulatory range" – within this range of perfusion pressures, the brain can modify regional vascular resistance (RVR) in order to keep blood flow relatively constant.[3] As with all tissues, the brain contains arteries, capillaries, and veins and the blood that is present in the brain can be divided into these three theoretical compartments.[4] Changes in cerebral vascular tone that impact RVR also change vessel compliance, which can alter the ratio of these compartments.[5] Variables that affect cerebral RVR include $PaCO_2$, pH, and extreme hypoxia [**Figure 1**].[6] Changes in adrenergic tone as well as temperature can also impact cerebral RVR although the mechanism(s) are incompletely understood and in some cases, controversial. [6-8]

The ultimate physiologic goal of a cerebral oximeter is to give the user some indirect indication of the cerebral tissue oxygen saturation (StO_2). This makes cerebral oximetry different from pulse oximetry, the goal of which is to determine the oxygen saturation in arterial *blood*. Because blood (i.e., hemoglobin) oxygenation is not a direct measure of tissue oxygenation, early cerebral oximeters attempted to measure the oxidation state of cytochrome aa_3, the terminal component of the mitochondrial electron chain (called Cyt_{OX}).[9] In theory, Cyt_{OX} could provide investigators (and clinicians) with information regarding the adequacy of oxygen supply and demand in brain tissue itself.

Unfortunately, because of cytochrome aa_3 exists in lower concentrations than hemoglobin and because it more weakly absorbs near infrared (NIR) radiation, accurately measuring Cyt_{OX} is challenging and requires broadband devices which are not available for clinical use.[10]

Cerebral oximetry utilizes NIRS to measure the relative concentration of "chromophores" (i.e., biological molecules that absorb electromagnetic radiation [EMR]), based on the modified Beer-Lambert Law for a scattering medium which states[11,12]:

$$\mathbf{OD_\lambda = \varepsilon_\lambda \bullet L \bullet c \bullet DPF + OD_{R,\lambda},}$$

where, OD_λ is the optical density of a medium, ε_λ represents the extinction coefficient of a chromophore, L represents the source-detector separation, c represents the concentration of the chromophore, DPF (differential pathlength factor) represents a correction factor designed to estimate how far a photon actually travels through tissue, and $OD_{R,\lambda}$ represents a geometry and wavelength-dependent correction factor. Of note DPF is dependent on the absorption coefficient of tissue, the scattering coefficient, and L, and is wavelength-dependent.[13] When *changes* in concentration are desired, this equation can be simplified to $\Delta c = \Delta OD_\lambda / (\varepsilon_\lambda \bullet L \bullet DPF)$ for one chromophore as OD_R is a constant and drops out. To determine the concentration of multiple chromophores (e.g., oxyhemoglobin and deoxyhemoglobin), a set of equations (one for each wavelength) can be solved simultaneously using matrix algebra [**Figure 2**]. Of note, actual concentrations of chromophores cannot be measured unless ε_λ, L, and DPF are known. While some research devices are capable of estimating the DPF and providing absolute measures of chromophore concentrations, FDA-approved devices are not.[14] *Therefore, cerebral oximetry measurements must be viewed as relative measures, not*

absolute values. Accordingly, the changes in $SctO_2$ relative to baseline (i.e., pre-induction of anesthesia) measurements offer more clinical information that complements absolute measurements.

Modern cerebral oximeters use spatially resolved spectroscopy (SRS) to focus their measurements on the brain. EMR is transmitted into the brain through the skull, and photons travel in stochastic (predictable only on a probabilistic basis) fashion through skin, muscle, fat, bone (skull), meninges, and brain. Photon detectors (e.g. photodiodes) are placed 2-4 cm away from the light source, serving to detect photons that are reflected by tissues in their path. In order to separate the absorbance of the brain chromophores from the absorbance of other extracranial tissue chromophores, the stronger, more proximal signal (lower absorbance) is subtracted from the weaker distal signal (higher absorbance). Both signals are affected equally by skin, muscle, fat, and bone, and the difference between the two signals is therefore due to absorbance through the brain.[15] [**Figure 3**]

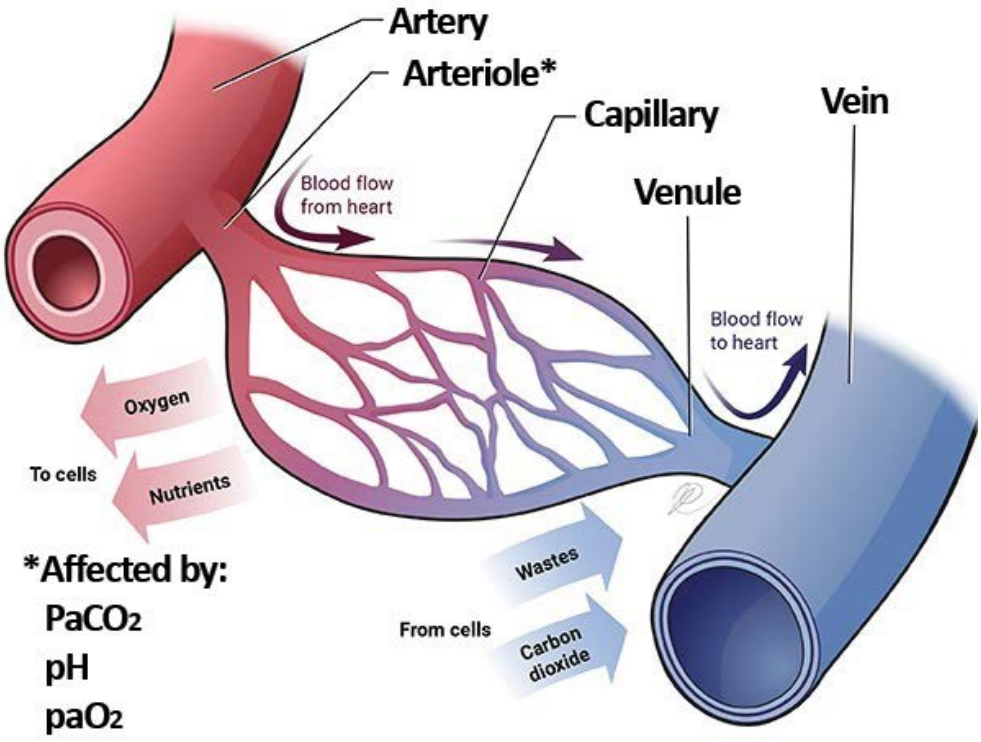
As noted in the manuscript, commercially available cerebral oximeters are therefore only capable of measuring the relative amount of oxygenated hemoglobin in an "optical field" interrogated using SRS-NIRS. Furthermore, SRS-NIRS analyzes all light absorbed by the brain and other tissues, as compared to pulse oximeters which only analyze pulsatile (arterial) absorbance. The "tissue saturation" of the blood in the brain measured by a cerebral oximeter is a combination of arterial, capillary, and venous blood. If one assumes that arterial oxygen saturation is close to 100%, that the volume of capillary blood is relatively small, and that the relative volume (or ratio) of arterial and venous blood is fixed (e.g. 30:70, or 25:75, depending on the device

manufacturer), the oxygenation of venous blood leaving the cerebral capillary beds can be estimated using the following equation:

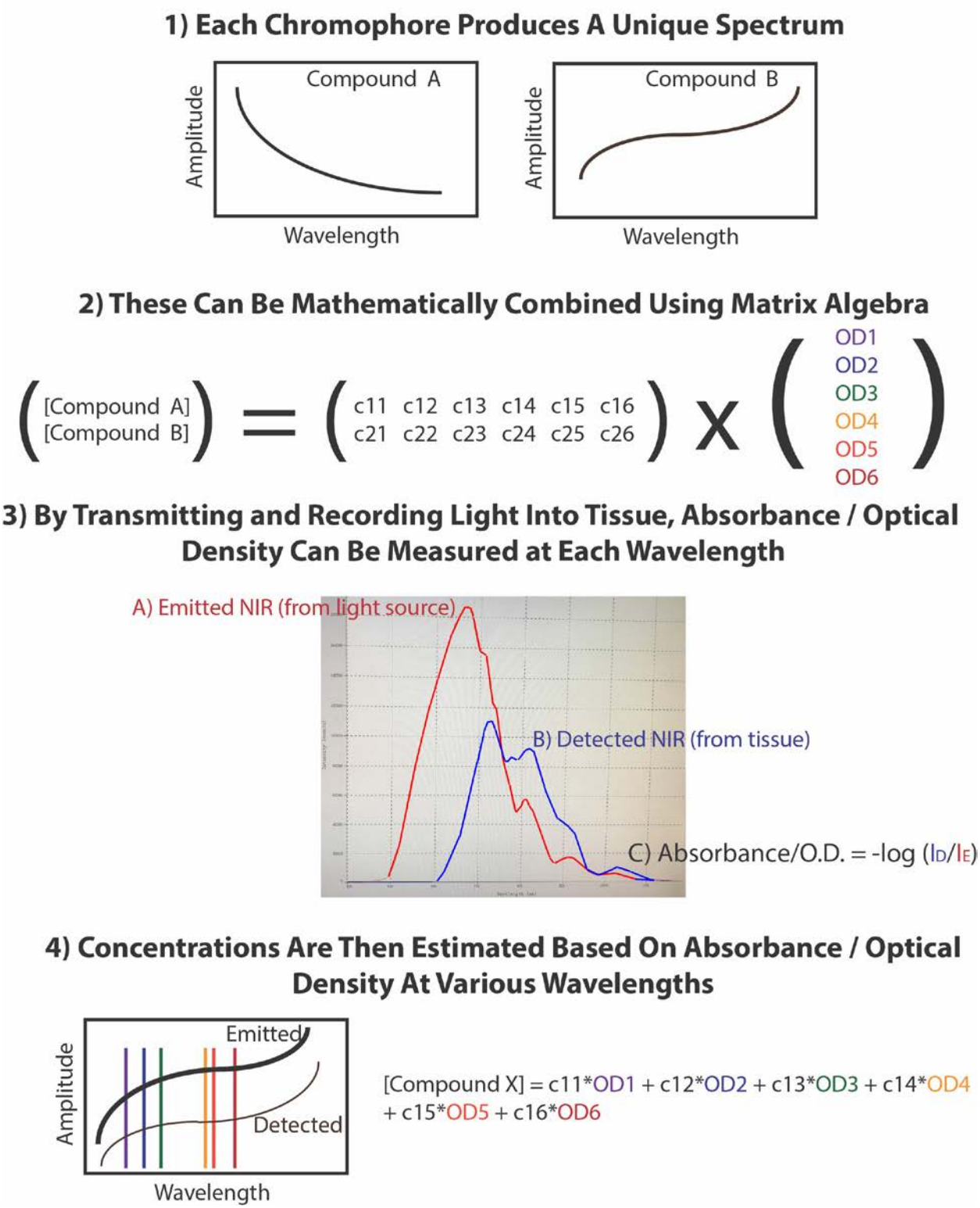
$$\mathbf{S_{venous,cerebral}O_2 = (S_{tissue}O_2 - 0.3*100\%)/(0.7)}$$

In fact, commercially available cerebral oximeters are often validated against measurements of jugular bulb oxygen saturation during staged hypoxia protocols or in patients requiring extracorporeal support.[16,17] In that sense, they could be more accurately viewed as non-invasive jugular venous bulb monitors, not tissue oximeters per se. Indeed, direct comparisons of cerebral or jugular hemoglobin saturation and brain tissue PO_2 using invasive measures (Clarke electrode) have found very little relationship between the two.[18-20] Therefore, as stated above, commercially available cerebral oximeters all assume a fixed arterial:venous ratio (the true percentage of venous blood can range from 33-84%) and the arterial:venous ratio is affected by many variables.[5,21,22]

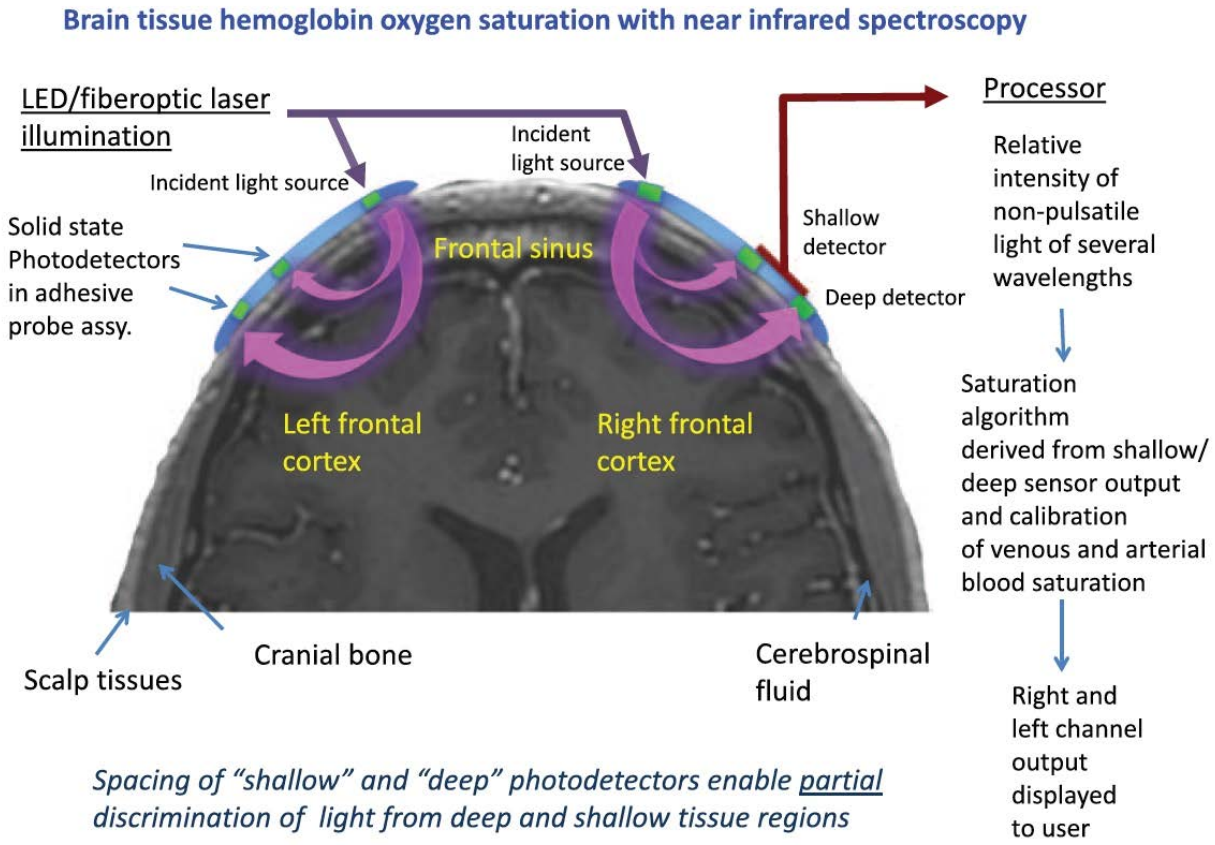
Appendix 3, Figure 1



Appendix 3 , Figure 2



Appendix 3, Figure 3



Appendix 3, Figure 1. Cerebral Blood Flow: an important feature of cerebral oximeters is their inability to differentiate between arterial, capillary, and venous blood. Red and infrared light are transmitted through, and absorbed by, arterial, capillary, and venous blood indiscriminately. Changes in the relative sizes of these compartments can therefore change the cerebral saturation calculation.

Appendix 3, Figure 2. How NIRS Works (Mathematics): cerebral oximeters use matrix algebra to estimate the relative concentration of distinct chromophores (e.g. oxy-hemoglobin, deoxy-hemoglobin). At least one wavelength of light is needed for each chromophore. Thus, at a minimum, a cerebral oximeter requires two wavelengths of light.

Appendix 3, Figure 3. How NIRS Works (Mechanics): in order to estimate the concentration of oxy-hemoglobin, deoxy-hemoglobin in the brain, cerebral oximeters utilize at least two sensors. Photons travel in a random path from their emitter, a light-emitting diode (LED), to each of the sensors. The "average" path of photons is affected by the distance between the LED and the sensors. Note that the path to the distal sensor passes through the brain, whereas the path to the proximal sensor does not. This difference allows these devices to mathematically remove the contribution of extracranial tissue to the calculation of ScO_2, although because photons follow random paths and not perfect arcs (as depicted in Figure 2), this process is imperfect. Figure from Bickler P. et al., "Tissue Oximetry and Clinical Outcomes", Anesth Analg 2017. Reproduced with permission.[23]

References for Appendix 3: Detailed Description of Near-Infrared Spectroscopy (NIRS) Devices

1. Thiele RH, Nemergut EC, Lynch C, 3rd. The Physiologic Implications of Isolated Alpha1 Adrenergic Stimulation. Anesth Analg. 2011.
2. Thiele RH, Nemergut EC, Lynch C, 3rd. The Clinical Implications of Isolated Alpha(1) Adrenergic Stimulation. Anesth Analg. 2011;113:297-304.
3. Rivera-Lara L, Zorrilla-Vaca A, Geocadin RG et al. Cerebral Autoregulation-Oriented Therapy at the Bedside: A Comprehensive Review. Anesthesiology. 2017;126:1187-99.
4. Ito H, Kanno I, Iida H et al. Arterial Fraction of Cerebral Blood Volume in Humans Measured by Positron Emission Tomography. Ann Nucl Med. 2001;15:111-6.
5. Ito H, Ibaraki M, Kanno I et al. Changes in the Arterial Fraction of Human Cerebral Blood Volume During Hypercapnia and Hypocapnia Measured by Positron Emission Tomography. J Cereb Blood Flow Metab. 2005;25:852-7.
6. Willie CK, Tzeng YC, Fisher JA et al. Integrative Regulation of Human Brain Blood Flow. J Physiol. 2014;592:841-59.
7. Cheng W, Hartmann JF, Cameron DE et al. Cerebral Blood Flow During Cardiopulmonary Bypass: Influence of Temperature and Ph Management Strategy. Ann Thorac Surg. 1995;59:880-6.
8. Wilson TE, Cui J, Zhang R et al. Heat Stress Reduces Cerebral Blood Velocity and Markedly Impairs Orthostatic Tolerance in Humans. Am J Physiol Regul Integr Comp Physiol. 2006;291:R1443-8.
9. Jobsis FF. Noninvasive, Infrared Monitoring of Cerebral and Myocardial Oxygen Sufficiency and Circulatory Parameters. Science. 1977;198:1264-7.

10. Grocott HP, Thiele RH. Brain Tissue Oximetry: What Are We Really Measuring? Anesth Analg. 2017;124:2091-2.
11. Wyatt JS, Cope M, Delpy DT et al. Quantitation of Cerebral Blood Volume in Human Infants by near-Infrared Spectroscopy. J Appl Physiol (1985). 1990;68:1086-91.
12. Talukdar T, Moore JH, Diamond SG. Continuous Correction of Differential Path Length Factor in near-Infrared Spectroscopy. J Biomed Opt. 2013;18:56001.
13. Scholkmann F, Wolf M. General Equation for the Differential Pathlength Factor of the Frontal Human Head Depending on Wavelength and Age. J Biomed Opt. 2013;18:105004.
14. Wolf M, Franceschini MA, Paunescu LA et al. Absolute Frequency-Domain Pulse Oximetry of the Brain: Methodology and Measurements. Adv Exp Med Biol. 2003;530:61-73.
15. Quaresima V, Sacco S, Totaro R et al. Noninvasive Measurement of Cerebral Hemoglobin Oxygen Saturation Using Two near Infrared Spectroscopy Approaches. J Biomed Opt. 2000;5:201-5.
16. Naguib AN, Winch PD, Sebastian R et al. The Correlation of Two Cerebral Saturation Monitors with Jugular Bulb Oxygen Saturation in Children Undergoing Cardiopulmonary Bypass for Congenital Heart Surgery. J Intensive Care Med. 2017;32:603-8.
17. Benni PB, MacLeod D, Ikeda K et al. A Validation Method for near-Infrared Spectroscopy Based Tissue Oximeters for Cerebral and Somatic Tissue Oxygen Saturation Measurements. J Clin Monit Comput. 2018;32:269-84.

18. Gopinath SP, Valadka AB, Uzura M et al. Comparison of Jugular Venous Oxygen Saturation and Brain Tissue Po2 as Monitors of Cerebral Ischemia after Head Injury. Crit Care Med. 1999;27:2337-45.
19. Gupta AK, Hutchinson PJ, Al-Rawi P et al. Measuring Brain Tissue Oxygenation Compared with Jugular Venous Oxygen Saturation for Monitoring Cerebral Oxygenation after Traumatic Brain Injury. Anesth Analg. 1999;88:549-53.
20. Rosenthal G, Furmanov A, Itshayek E et al. Assessment of a Noninvasive Cerebral Oxygenation Monitor in Patients with Severe Traumatic Brain Injury. J Neurosurg. 2014;120:901-7.
21. Benni PB, Chen B, Dykes FD et al. Validation of the Cas Neonatal Nirs System by Monitoring Vv-Ecmo Patients: Preliminary Results. Adv Exp Med Biol. 2005;566:195-201.
22. Watzman HM, Kurth CD, Montenegro LM et al. Arterial and Venous Contributions to near-Infrared Cerebral Oximetry. Anesthesiology. 2000;93:947-53.
23. Bickler P, Feiner J, Rollins M et al. Tissue Oximetry and Clinical Outcomes. Anesth Analg. 2017;124:72-82.

Supplemental Tables

Supplemental Table 1: Pre-operative Baseline ScO_2 and Outcomes

Author	Year	Population	n	Oximeter	Outcomes (in low ScO_2 group)
Heringlake[1]	2011	Cardiac surgery	1178	INVOS 4100 or 5100	Increased 30-day mortality; composite [RRT, re-intubation, stroke, low CI, prolonged LOS]
Schoen[2]	2011	Cardiopulmonary bypass	231	INVOS 5100	Increased delirium
Sun[3]	2014	Cardiac surgery	2097	INVOS 5100c	Higher risk-adjusted mortality
Lei[4]	2017	Cardiopulmonary bypass	249	INVOS 5100c	Increased delirium (note, secondary analysis in negative RCT)
Ghosal[5]	2018	Left Ventricular Assist Device	210	INVOS 5100c	Increased 30-day mortality

Supplemental Table 2: Case Reports of Intraoperative Use of Cerebral Oximetry

Author	Year	Population	Oximeter	Findings
Aono*[6]	1998	Aortic surgery	INVOS 3100	ScO_2 measurements were lower during circulatory arrest and increased to or above baseline during SCP (2 patients).
Blas[7]	1999	Aortic arch replacement	INVOS 3100	Persistently reduced ScO_2 prompted inspection of a malpositioned retrograde cerebral perfusion cannula. Following repositioning, ScO_2 returned towards baseline.
Janelle[8]	2002	Repair of DeBakey type 1 aortic dissection	INVOS 5100	Reduced ScO_2 values during CPB led to surgical exploration identifying an extension of a false lumen into the carotid artery resulting in inadequate hemispheric cerebral blood flow. This was then surgically repaired.
Prabhune[9]	2002	Coronary artery bypass grafting	INVOS 4100	Reduced ScO_2 values during CPB led to identification of a gas leak from an anesthetic vaporizer manifold.
Sugawara[10]	2002	Ascending to infrarenal aortic bypass grafting	TOS-96 (TOSTEC)	ScO_2 monitoring was utilized to guide rate of CPB flow to both reduce aortic pressure and prevent brain ischemia in complex surgery.
Han[11]	2005	Total correction of tetralogy of Fallot	INVOS 5100	ScO_2 monitoring led to identification of a malpositioned superior vena cava cannula that was successfully repositioned.
Aron[12]	2007	Coronary artery bypass grafting, mitral valve repair, modified MAZE procedure	INVOS 5100B	Reduced ScO_2 measurements were attributed to Raynoud's disease episodes and managed with nitroglycerin administration.
Kasahara[13]	2007	Mitral valve repair	NIRO-200	During CPB without aortic cross-clamping, aortic regurgitation during retraction of the atrial septum complicated surgical exposure. Hypothermic CPB with low flow was guided by monitoring of ScO_2 values.
Cheng[14]	2008	Aortic arch replacement	INVOS 5100B	ScO_2 trends were used to optimize cerebral perfusion and to confirm the patency of the surgical graft anastomosis.
Fujiwara[15]	2008	Mitral valve replacement (re-do)	Unknown	Reduced ScO_2 was associated with anaphylactic shock caused by aprotinin.
Hassan[16]	2010	Mitral valve and aortic valve replacement	ForeSight®	A persistent left superior vena cava was incidentally found during surgery. ScO_2 monitoring was used to indicate adequate cerebrovascular venous drainage following occlusion of the persistent left superior vena cava.
Paarmann[17]	2010	Transapical aortic valve replacement	INVOS 5100	During cardiopulmonary resuscitation ScO_2 trended in parallel with mixed venous oximetry.
Faulkner[18]	2011	Coronary artery bypass grafting, aortic valve replacement, mitral valve repair	ForeSight®	Reduced ScO_2 led to identification of a malpositioned superior vena cava cannula. Upon correcting its position, ScO_2 values returned to baseline.
Vernick[19]	2011	Coronary artery bypass grafting, aortic valve replacement, mitral valve repair	INVOS 5100	Reduced ScO_2 values following repair of the superior vena cava decannulation site after CPB led to diagnosis and subsequent repair of iatrogenic superior vena cava obstruction.
Chan[20]	2014	Repair of type-A aortic dissection	INVOS	ScO_2 monitoring identified a malpositioned catheter used for antegrade cerebral perfusion during deep hypothermic circulatory arrest.
Yamasaki*[21]	2017	Ross procedure	Unknown	Low ScO_2 led to identification and repositioning of an aortic CPB cannula that had erroneously been placed in the left subclavian artery.

DHCA=Deep Hypothermic Circulatory Arrest; SCP=Selective Cerebral Perfusion

*Article in Japanese – only the English-language abstract was reviewed. Table was adapted from Zheng 2013 (PMID 23267000) with additions.

Supplemental Table 3: Relationship Between Intraoperative Cerebral Desaturation and Outcomes

Study	n	Oximeter	Outcome / test	Association between low (absolute) or decreased (trend) ScO_2 and outcome	Comments
Reents[22]	47	INVOS 4100	cognitive decline (multiple tests)	No	ScO2 monitoring started after induction
Yao[23]	101	INVOS 4100	MMSE and ASEM 4-6 d post-OP	Yes	ScO2 cutoff 40%
Negargar[24]	72	INVOS 4100	MMSE 24h post-OP	No	Unplausible design
Hong[25]	100	INVOS 5100	Cognitive decline (various tests) / length of stay	No / Yes	LoS secondary outcome
Slater[26]	240	INVOS 5100	Cognitive decline (various tests) / length of stay	Yes	Change in study objectives from RCT to observational. Utilized a detaturation score indexing current ScO_2 to average ScO_2 throughout the procedure
de Tournay-Jetté[27]	61	INVOS 5100	Cognitive decline (various tests)	Yes	1 month follow up
Schoen[28]	128	INVOS 5100	Cognitive decline (various tests)/complications	Yes /Yes	RCT – Sevoflurane vs. propofol - ScO2 effects detectable only in the TIVA group
Schoen[2]	231	INVOS 5100	Delirium / CAM/ICU	Yes	ScO2 effects detectable only in the pts. with ScO2 > 59.5%
Fischer[29]	30	Foresight	Major complications	Yes	Dose dependent association between area under desaturation thresholds and complications
Kok[30]	60	INVOS 5100	Cognitive decline (multiple tests)	No	RCT of Off vs. On-pump CABG - only 3 patients with ScO2 < 40% for > 10 min.
Colak[31]	190	INVOS 5100	Three cognitive function tests	Yes / Yes	Secondary analysis of RCT
Mukaida [32]	573	INVOS 5100	Mortality	Yes / No	Baseline and lowest ScO2 were correlated with mortality, but not relative ScO2

Supplemental Table 4: Randomized Controlled Trials of Cerebral Oximetry in Cardiac Surgery

Study	Year	n	Outcome / test	Positive effect of cerebral oximetry	Oximeter	Comments
Murkin[33]	2007	200	MOMM	Yes	INVOS 5100	Marginally significant combined endpoint
Mohandas[34]	2013	100	MMSE / ASEM/ICU LOS	Yes	EQUANOX 7600	3 month follow up
Vretzakis[35]	2013	150	No. of transfused PRC	Yes	INVOS 5100	No oximetry in the control group
Colak[31]	2014	190	Cognitive decline (multiple tests) / LOS	Yes	INVOS 5100	No oximetry in the control group
Harilall[36]	2014	40	S100 beta	Yes	INVOS 5100	No information on outcome
Kara[37]	2015	79	Cognitive decline (multiple tests) / LOS	Yes	INVOS 5100	No oximetry in the control group
Deschamps[38]	2016	201	Reversibility of cerebral desaturation / morbidity and mortality	No	Multiple cerebral oximeters	Multicenter trial using different oximeters but a treatment algorithm developed for the INVOS oximeter (note: pilot study not powered for outcomes)
Lei[4]	2017	249	Delirium / CAM-ICU	No	INVOS 5100	Baseline ScO2 predictive of delirium / 50% of patients premedicated with lorazepam / use of benzodiazepines intraoperative up to 0.05 mg/kg allowed but not reported
Rogers[39]	2017	208	Cognitive decline (multiple tests) / morbidity and mortality	No	INVOS 5100	Different minimal hematocrit goals in the control and intervention group / “generic- algorithm” in the control group not defined / intervention period limited to CPB period

References for Supplemental Digital Content - Supplemental Tables 1-4

1. Heringlake M, Garbers C, Kabler JH et al. Preoperative Cerebral Oxygen Saturation and Clinical Outcomes in Cardiac Surgery. Anesthesiology. 2011;114:58-69.

2. Schoen J, Meyerrose J, Paarmann H et al. Preoperative Regional Cerebral Oxygen Saturation Is a Predictor of Postoperative Delirium in on-Pump Cardiac Surgery Patients: A Prospective Observational Trial. Crit Care. 2011;15:R218.

3. Sun X, Ellis J, Corso PJ et al. Mortality Predicted by Preinduction Cerebral Oxygen Saturation after Cardiac Operation. Ann Thorac Surg. 2014;98:91-6.

4. Lei L, Katznelson R, Fedorko L et al. Cerebral Oximetry and Postoperative Delirium after Cardiac Surgery: A Randomised, Controlled Trial. Anaesthesia. 2017;72:1456-66.

5. Ghosal S, Trivedi J, Chen J et al. Regional Cerebral Oxygen Saturation Level Predicts 30-Day Mortality Rate after Left Ventricular Assist Device Surgery. J Cardiothorac Vasc Anesth. 2018;32:1185-90.

6. Aono M, Sata J, Nishino T. [Regional Cerebral Oxygen Saturation as a Monitor of Cerebral Oxygenation and Perfusion During Deep Hypothermic Circulatory Arrest and Selective Cerebral Perfusion]. Masui. 1998;47:335-40.

7. Blas ML, Lobato EB, Martin T. Noninvasive Infrared Spectroscopy as a Monitor of Retrograde Cerebral Perfusion During Deep Hypothermia. J Cardiothorac Vasc Anesth. 1999;13:244-5.

8. Janelle GM, Mnookin S, Gravenstein N et al. Unilateral Cerebral Oxygen Desaturation During Emergent Repair of a Debakey Type 1 Aortic Dissection: Potential Aversion of a Major Catastrophe. Anesthesiology. 2002;96:1263-5.

9. Prabhune A, Sehic A, Spence PA et al. Cerebral Oximetry Provides Early Warning of Oxygen Delivery Failure During Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 2002;16:204-6.

10. Sugawara Y, Sueda T, Orihashi K et al. Surgical Treatment of Atypical Aortic Coarctation Associated with Occlusion of All Arch Vessels in Takayasu's Disease. Eur J Cardiothorac Surg. 2002;22:836-8.

11. Han SH, Kim CS, Lim C et al. Obstruction of the Superior Vena Cava Cannula Detected by Desaturation of the Cerebral Oximeter. J Cardiothorac Vasc Anesth. 2005;19:420-1.

12. Aron JH, Fink GW, Swartz MF et al. Cerebral Oxygen Desaturation after Cardiopulmonary Bypass in a Patient with Raynaud's Phenomenon Detected by near-Infrared Cerebral Oximetry. Anesth Analg. 2007;104:1034-6, tables of contents.

13. Kasahara H, Shin H, Mori M. Cerebral Perfusion Using the Tissue Oxygenation Index in Mitral Valve Repair in a Patient with Porcelain Aorta and Aortic Regurgitation. Ann Thorac Cardiovasc Surg. 2007;13:413-6.

14. Cheng HW, Chang HH, Chen YJ et al. Clinical Value of Application of Cerebral Oximetry in Total Replacement of the Aortic Arch and Concomitant Vessels. Acta Anaesthesiol Taiwan. 2008;46:178-83.

15. Fujiwara Y, Matsuura S, Fukuda K. [Case of Aprotinin-Induced Anaphylactic Shock]. Masui. 2008;57:366-9.

16. Hassan MA, Rozario C, Elsayed H et al. A Novel Application of Cerebral Oximetry in Cardiac Surgery. Ann Thorac Surg. 2010;90:1700-1.

17. Paarmann H, Heringlake M, Sier H et al. The Association of Non-Invasive Cerebral and Mixed Venous Oxygen Saturation During Cardiopulmonary Resuscitation. Interact Cardiovasc Thorac Surg. 2010;11:371-3.

18. Faulkner JT, Hartley M, Tang A. Using Cerebral Oximetry to Prevent Adverse Outcomes During Cardiac Surgery. Perfusion. 2011;26:79-81.

19. Vernick WJ, Oware A. Early Diagnosis of Superior Vena Cava Obstruction Facilitated by the Use of Cerebral Oximetry. J Cardiothorac Vasc Anesth. 2011;25:1101-3.

20. Chan SK, Underwood MJ, Ho AM et al. Cannula Malposition During Antegrade Cerebral Perfusion for Aortic Surgery: Role of Cerebral Oximetry. Can J Anaesth. 2014;61:736-40.

21. Yamasaki A, Hino M, Maekawa S et al. [a Case of Aortic Cannula Malposition Detected by Prolonged Desaturation of Regional Cerebral Oxygen Index (Rcso(2))]. Masui. 2017;66:131-4.

22. Reents W, Muellges W, Franke D et al. Cerebral Oxygen Saturation Assessed by near-Infrared Spectroscopy During Coronary Artery Bypass Grafting and Early Postoperative Cognitive Function. Ann Thorac Surg. 2002;74:109-14.

23. Yao FS, Tseng CC, Ho CY et al. Cerebral Oxygen Desaturation Is Associated with Early Postoperative Neuropsychological Dysfunction in Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2004;18:552-8.

24. Negargar S, Mahmoudpour A, Taheri R et al. The Relationship between Cerebral Oxygen Saturation Changes and Post Operative Neurologic Complications in Patients Undergoing Cardiac Surgery. Pak J Med Sci. 2007;23:380-5.

25. Hong SW, Shim JK, Choi YS et al. Prediction of Cognitive Dysfunction and Patients' Outcome Following Valvular Heart Surgery and the Role of Cerebral Oximetry. Eur J Cardiothorac Surg. 2008;33:560-5.

26. Slater JP, Guarino T, Stack J et al. Cerebral Oxygen Desaturation Predicts Cognitive Decline and Longer Hospital Stay after Cardiac Surgery. Ann Thorac Surg. 2009;87:36-44; discussion -5.

27. de Tournay-Jette E, Dupuis G, Bherer L et al. The Relationship between Cerebral Oxygen Saturation Changes and Postoperative Cognitive Dysfunction in Elderly Patients after Coronary Artery Bypass Graft Surgery. J Cardiothorac Vasc Anesth. 2011;25:95-104.

28. Schoen J, Husemann L, Tiemeyer C et al. Cognitive Function after Sevoflurane- Vs Propofol-Based Anaesthesia for on-Pump Cardiac Surgery: A Randomized Controlled Trial. Br J Anaesth. 2011;106:840-50.

29. Fischer GW, Lin HM, Krol M et al. Noninvasive Cerebral Oxygenation May Predict Outcome in Patients Undergoing Aortic Arch Surgery. J Thorac Cardiovasc Surg. 2011;141:815-21.

30. Kok WF, van Harten AE, Koene BM et al. A Pilot Study of Cerebral Tissue Oxygenation and Postoperative Cognitive Dysfunction among Patients Undergoing Coronary Artery Bypass Grafting Randomised to Surgery with or without Cardiopulmonary Bypass*. Anaesthesia. 2014;69:613-22.

31. Colak Z, Borojevic M, Bogovic A et al. Influence of Intraoperative Cerebral Oximetry Monitoring on Neurocognitive Function after Coronary Artery Bypass Surgery: A Randomized, Prospective Study. Eur J Cardiothorac Surg. 2015;47:447-54.

32. Mukaida H, Hayashida M, Matsushita S et al. Brain Natriuretic Peptide (Bnp) May Play a Major Role in Risk Stratification Based on Cerebral Oxygen Saturation by near-Infrared Spectroscopy in Patients Undergoing Major Cardiovascular Surgery. PLoS One. 2017;12:e0181154.

33. Murkin JM, Adams SJ, Novick RJ et al. Monitoring Brain Oxygen Saturation During Coronary Bypass Surgery: A Randomized, Prospective Study. Anesth Analg. 2007;104:51-8.

34. Mohandas BS, Jagadeesh AM, Vikram SB. Impact of Monitoring Cerebral Oxygen Saturation on the Outcome of Patients Undergoing Open Heart Surgery. Ann Card Anaesth. 2013;16:102-6.

35. Vretzakis G, Georgopoulou S, Stamoulis K et al. Monitoring of Brain Oxygen Saturation (Invos) in a Protocol to Direct Blood Transfusions During Cardiac Surgery: A Prospective Randomized Clinical Trial. J Cardiothorac Surg. 2013;8:145.

36. Harilall Y, Adam JK, Biccard BM et al. The Effect of Optimising Cerebral Tissue Oxygen Saturation on Markers of Neurological Injury During Coronary Artery Bypass Graft Surgery. Heart Lung Circ. 2014;23:68-74.

37. Kara I, Erkin A, Sacli H et al. The Effects of near-Infrared Spectroscopy on the Neurocognitive Functions in the Patients Undergoing Coronary Artery Bypass Grafting with Asymptomatic Carotid Artery Disease: A Randomized Prospective Study. Ann Thorac Cardiovasc Surg. 2015;21:544-50.

38. Deschamps A, Hall R, Grocott H et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation During High-Risk Cardiac Surgery: A Randomized Controlled Feasibility Trial. Anesthesiology. 2016;124:826-36.

39. Rogers CA, Stoica S, Ellis L et al. Randomized Trial of near-Infrared Spectroscopy for Personalized Optimization of Cerebral Tissue Oxygenation During Cardiac Surgery. Br J Anaesth. 2017;119:384-93.