Near Infra-Red Spectroscopy in a Pediatric Population Undergoing Cardiac Surgery

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Abstract

Background: Intraoperative Near Infra-Red Spectroscopy (NIRS) may reduce postoperative neurologic complications. Use in pediatric populations, NIRS increases, and variations in sensor placement are understudied.

Objective: To explore NIRS performance in a pediatric population undergoing cardiac surgery; to describe significant (20%) NIRS deviations from baseline; to correlate events with physiologic variables; to examine the relevance of a second sensor.

Methods: Retrospective review of prospectively collected NIRS data. Associations were assessed using Student's t-test, chi-squared test and logistic regression.

Results: Significant deviations from baseline were common. Many occurred when unsupported by CPB (cardiopulmonary bypass) or upon CPB initiation. NIRS decreases and increases were significantly associated with P_aO_2, hematocrit, and MAP (mean arterial pressure) ($p<0.05$) and p_aCO_2 ($p<0.01$), respectively. Unilateral deviations were frequent, particularly amongst cyanotic and male patients.

Conclusion: In this population, significant NIRS deviations are associated with physiologic variables. A second sensor provided significant information.

Introduction: Le Near Infra-Red Spectroscopy (NIRS) utilitisé durant la période opératoire peut réduire les complications neurologiques postopératoires. L'utilisation du NIRS chez la population pédiatrique et les variations associées au placement des senseurs sont sous étudiées.

Objectifs: Explorer les performances du NIRS chez les enfants lors de chirurgies cardiaques; décrire les variations significatives du NIRS (20%) en comparaison aux niveaux témoins; établir des corrélations entre les événements et les variables mesurées; établir l'utilité d'un second senseur.

Méthodes: Une revue rétrospective de données NIRS obtenues de façon prospective. Les relations observées seront évaluées avec les tests Student-t, chi-squared, et de régression logistique.

Résultats: Des variations significatives en comparaison aux valeurs témoins ont été observées. Plusieurs de ces variations ont eu lieu lorsque les patients n'étaient pas supportés par la circulation extracorporelle ou lors de son initiation. Les augmentations et diminutions du NIRS sont significativement reliées au P_aO_2, à l'hématocrite, à la pression artérielle moyenne ($p<0.05$) et au p_aCO_2 ($p<0.01$), respectivement. Des variations unilatérales du NIRS sont fréquentes, particulièrement chez les patients cyanosés et chez les patients males.

Conclusion: Chez cette population pédiatrique, des déviations significatives du NIRS sont associées à certaines variables physiologiques. Le deuxième senseur ajoute des informations utiles.

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Introduction

The goal of this thesis is to deepen our understanding of neuromonitoring technology in a pediatric population undergoing cardiac surgery by examining the behaviour of one such monitoring technology and determining its associations with physiologic variables. The fundamental objective of the use of such technology is to improve post-operative outcomes; however more information about the physiologic relevance of these monitors is required. The neuromonitoring technology of central interest to this thesis is near-infrared spectroscopy, henceforth NIRS. NIRS is becoming a commonly utilized neuromonitor, with some authors going so far as to call it standard of care.[1,2] It serves to identify potential critical periods of cerebral tissue injury which might be averted with responses by medical personnel, however it has not been fully evaluated in the pediatric population, among whom neurologic sequelae of cardiac surgery are prevalent.[3]

The introduction will serve to provide an overview of the history and fundamentals of cardiac surgery. Next, the topic of post-operative neurological deficits in this population will be discussed. This will include a review of the literature documenting, qualifying and quantifying such deficits, as well as a discourse on possible timing and causes of their occurrence. Penultimately, information concerning several alternative intraoperative neuromonitoring techniques will be summarized. Finally we will review the literature specific to NIRS; this will include an explanation of the physics behind the technology, a comparison of the machines currently available and an assessment of previous studies in which NIRS was used.

The methods section follows, and will explore the study methods in greater detail than can be permitted in the papers, from a critical epidemiological point of view.

Following the introduction and methods section, three manuscripts will be presented reviewing the work done for this thesis on NIRS monitoring. The objective of these manuscripts is to provide further information on NIRS monitoring in a pediatric population undergoing cardiac surgery. The first reviews physiologic variables associated with low NIRS events. The second deals with physiologic variables associated with high NIRS events. By demonstrating that both low and high events are associated with measures known to affect cerebral oxygen supply and demand, we demonstrate that the technology manifests at least some dimensions of face validity. The third paper addresses the issue of bilateral vs. unilateral monitoring. This paper is key in attempting to establish a context for future research. Finally, a discussion and conclusion will review the principal observations, strengths and weaknesses of the work as well as it potential implications.

Pediatric Cardiac Surgery

Approximately 1% of children are born with a heart defect[4]; this is termed congenital heart disease. There is a wide range of such disease: simple, and less severe, pathologies include small holes between cardiac compartments (atrial septal defects or ventricular septal defects); severe pathologies are uniformly fatal if left untreated, and include hypoplastic left heart syndrome (a complex cardiac anomaly wherein the left side of the heart is not fully developed), Tetralogy of Fallot (a classic lesion characterized by right ventricular hypertrophy, right ventricular outflow tract obstruction, a ventricular septal defect and an overriding aorta), and others. Fortunately, of the 1% of children born with cardiac pathologies, only a minority are sufficiently severe to require operative intervention for immediate or long-term survival. [5]

The ability to intervene surgically on these patients has only existed for approximately 50 years. Prior to the 1950s, there had been recognition of congenital cardiac pathologies, as well as some attempts to address them surgically. In fact, the first successful pediatric cardiac surgery was performed on a 7-year-old girl with a patent ductus arteriosus, by Dr. Gross in 1938.[6] In the 1940s, both he and Dr. Crafoord successfully addressed coarctation of the aorta.[7,8] However, whenever the pathology required intracardiac repair, opening the heart and arresting circulation for a period of time became a major dilemma. Thus, for the most part, the era of cardiac surgery began in 1954 with the advent of the cardiopulmonary bypass machine.

The cardiopulmonary bypass (CPB) machine, as invented by Gibbon, functioned to oxygenate and circulate the blood while the heart was arrested.[9] Simply put, the CPB machine is an extracorporeal mechanical device, which receives blood from the patient and pumps blood back to (and through) the patient, while excluding the heart from this circuit. Furthermore, it oxygenates the blood while removing carbon dioxide.

With the advent of CPB, open heart surgery became possible. Surgeons grasped the opportunity and began to approach a variety of cardiac defects previously deemed inoperable. Preliminary results, however, were poor for a number of reasons: the pump was quite large, and the priming volume of the circuit was essentially a massive blood transfusion, resulting in the release of many deleterious inflammatory mediators; microvascular instruments had not yet been invented, nor had the delicate surgical techniques to deal with fragile tissues; moreover, anesthesia and intensive care for young children was just beginning to develop and not yet capable of successfully handling the peri-operative course of many of these infants. Surgeons quickly realized that their patients' interests were best served by delaying their exposure to CPB as long as possible, and numerous surgical techniques were developed to serve that goal.[10]

Over the ensuing decades, technology and medicine advanced, and outcomes improved dramatically. Survival of young and small patients became the standard, rather than the exception. Interested parties began to study the morbidity of cardiac surgery at such a young age. At first, the major morbidity revolved around residual cardiac lesions, and intraoperative cardiac injury. With time however, new technologies such as echocardiography were developed and intraoperative results improved. Prolonged survival eventually revealed a new concern: neurological complications of cardiac surgery were both widely prevalent and significantly detrimental to quality of life[11]. In one report, a high prevalence of impairment was noted, including, but not limited to, intellectual dysfunction (low group mean IQ), specific language dysfunction, motor delays, behavior problems, and functional limitations.[12]

Following recognition of such significant neurocognitive morbidity associated with congenital cardiac surgery, understanding and optimizing neurological outcome became a focus for many researchers.[13,14,15,16] The Boston Circulatory Arrest Trial focused on patients undergoing repair of transposition of the great arteries.[17] In this study, they found that this population as a whole tested below expectations in assessments of academic achievement, fine motor function, higher-order language skills and ability to sustain attention.[18] Furthermore, at 8 years of age, half of the population had received remedial educational services, and 10% had repeated a grade.

More recently, investigators at the Montreal Children's Hospital have noted that, among infants undergoing cardiac surgery, 41% have abnormal neurological examinations 1-1.5 years post-operatively.[19] A significant number also demonstrated gross and fine motor delays (42%), or global developmental delays (23%). In a second study, the same investigators report that at school entry, 28% of patients with previously repaired congenital heart disease manifested neurological abnormalities.[20] A large proportion (49% and 39% respectively) demonstrated gross and fine motor skill deficiencies. Microcephaly was present in 15%. Hypotonia and developmental delay were also frequently noted (frequency not provided).

Injury Timeline

Several researchers have pursued the elucidation of possible timelines and pathophysiologies of these neurological and neurodevelopmental deficits. Grossly, these can be divided into pre-operative, peri-operative, and post-operative. There is evidence to support the occurrence of injury in each of these periods; the final developmental signature in any one child is likely the end result of a series of injurious experiences.

Pre-operatively, it has been noted that some children with congenital cardiac defects already present with an abnormal baseline. For example, more than half of newborns presenting to our institution for investigation of congenital heart disease did so with neurobehavioural and neurologic abnormalities.[21] These included hypotonia, jitteriness, motor asymmetries, feeding difficulties and poor state regulation. Another study examined this same cohort post-operatively, as well as an older cohort of infants.[22] A lesser, although still significant, proportion of infants (38%) demonstrated neurodevelopmental abnormalities pre-operatively. Importantly, in both age groups, pre-operative neurological status was an independent predictor of post-operative neurological status. [21,22]

Pre-operative neurologic abnormalities may originate in the prenatal period. Different intrauterine flow patterns appear to be associated with varying degrees of neurological injury. One study demonstrated that acyanotic patients were significantly more likely to exhibit neurobehavioural abnormalities than cyanotic patients.[23] The authors speculated that antenatal brain injury may be the result of altered cerebral perfusion, subsequently impairing autoregulation. Another antenatal source of cerebral dysfunction is the high rate of brain dysgenesis and other congenital CNS malformations that is seen in this population.[24] Another proposal is that some of the injury, or at least predisposition to injury, is genetic, even in the absence of syndromic pathologies. This is, in part, supported by Gaynor and Wernovsky's work demonstrating that a specific allele of the apolipoprotein (E2) is associated with worse neurological outcomes.[25]

Pre-operative injury may also occur postnatally. In the pre-operative period, congenital heart disease patients are at high risk for de novo brain injury. This generally takes the form of hypoxic-ischemic/reperfusion injury and germinal matrix – intraventricular hemorrhage.[26] Congenital cardiac patients are at high risk for hemodynamic instability, which places them at risk for both of these injury types. Moreover, decreased cardiac output (be it due to arrhythmias or structural impediments) and high degrees of left to right shunting tend to increase right-sided circulatory pressures. This in turn may reduce cerebral perfusion, via decreased cerebral venous drainage. It is as yet unclear how important these different mechanisms are. However, one study demonstrated a preoperative incidence of abnormalities on cranial ultrasound as high as 59%.[27]

There are also several potentially important factors in the peri-operative period. Pre-operative resuscitation and immediate post-operative care are likely important. Significant hemodynamic instability is associated with ischemic damage to the brain, much like a stroke, and this is known to occur in the peri-operative period. Intraoperatively, hypoxic-ischemic/reperfusion injury may occur as a result of global hypoperfusion or hypoxia or focal insults (due to vaso-occlusion, emboli, or inflammatory microvascular events).[28] Surgical strategies have been shown to be of some importance as well. Avoidance or minimization of deep hypothermic circulatory arrest (DHCA) improves neurological outcome[29]; hypoxic-ischemic/reperfusion injury during DHCA is delayed in onset and more prolonged in nature.[30] In addition, corrective operative approaches (wherein circulation patterns are rendered normal) are associated with better neuromotor and neurodevelopmental outcomes than palliative approaches (wherein circulation patterns remain abnormal, but physiologically improved).[31,32] Palliation, however, may be a marker for a constellation of confounders rather than an independent causal agent. More details on mechanisms of intraoperative injury will follow in the next section, as the focus of this thesis lies in intra-operative monitoring and its potential for injury prevention.

Finally, care during the post-operative period may also affect outcomes. Hemodynamics remain important, as brain cells, which have survived exposure to hypoxia/hypoperfusion, remain critically dependent on oxygen and energy supply to reestablish normal membrane protein function and intracellular ionic concentrations.[32] If this fails to occur, cells in the so-called penumbra region of the injury will perish as well, further extending injury.[33] Early rehabilitation may be associated with improved neurological outcome, or at least improved coping mechanisms.[34] Furthermore, long-term follow-up is necessary for the detection and treatment of any deficits. In summary, the neurologic injury and neurodevelopmental delay seen in many patients after congenital cardiac surgery may reflect the sequelae of injuries acquired pre- and post-natally, as well as peri- and intra-operatively.

Intraoperative Time Period and Monitoring

As described previously, there are multiple times at which brain injury may occur. We focus our attention now on the intraoperative time period, as studying neuromonitoring technique for intraoperative use will be the focus of the remainder of this thesis.

Intraoperative brain injury may be the result of focal or global insults. Focal insults are generally embolic or vasospastic. Global insults usually relate to pump flow rates, cerebral metabolic demand, hypothermia-related cerebral autovasoregulatory dysfunction, and acid-base imbalances. All have the same result: insufficient oxygen supply to the brain cells, with subsequent injury, and, if persistent, cell death. These phenomena are well detailed in a paper by du Plessis.[35]

The CPB machine recirculates material and fluid brought in during surgery by cannulae and suction devices. While the fluid does pass through a filter, this suffices to remove only macroscopic emboli; microscopic globules of fat, blood clot or pockets of gas may still be brought from the operating field into systemic circulation. Furthermore, the patient's immune system recognizes the artificial surfaces in the CPB circuit as foreign, further activating various components of the inflammatory cascades. These cascades result in increased leukocyte and platelet aggregation (clumping) and vasoregulatory dysfunction, further potential causes for hypoxic injury.[36]

Furthermore, it is important to realize that the CPB machine is capable of delivering flows less than, equal to, or greater than a patient's normal cardiac output. However, the patient's oxygen needs are likely reduced when anesthetized. Systemic adequacy of perfusion is well reflected by oxygen saturations in blood returning to the pump (excessive flow yields high values; insufficient flow yields low values). However, at present we have no proven method of assessing cerebral (or most other organ-specific) needs. Furthermore, flow rates are often affected by the surgeon's technical requirement for a blood-free operative field, despite patient metabolic needs. This latter situation presents the opportunity for insufficient or excessive cerebral blood flow.

Generally, patient cerebral oxygen requirements are determined by cerebral metabolic demands, which can be diminished via hypothermia and certain drugs, both of which are commonly utilized during cardiac surgery. However, our control is limited as cooling may be inhomogenous, and rewarming may occur faster than perfusion can support. Furthermore, use of hypothermia is limited by associated cardiac conduction disturbances post-operatively, and other sequelae. Also, most drugs have minimal activity once the patient is deeply hypothermic. Another related problem is that hypothermia causes a left shift of the oxyhemoglobin dissociation curve and increased blood viscosity, both of which increase microocclusion, decrease tissue oxygen supply, and may result in cellular injury. Thus it is very difficult to determine our success at matching cerebral oxygen supply to demand.

Furthermore, the CPB machine, despite all the advances in the last decades, remains a source of injury in adults via emboli, inflammatory mediators, and damage to circulating blood cells in the pump.[37] Given that the mechanisms effect injury in both adult and pediatric patients, it stands to reason that CPB may be a cause of neurological injury in pediatric patients as well.

A final mechanism of intraoperative cerebral cellular injury, which has been elucidated, relates to acid-base balance management. Intraoperatively, perfusionists (the CPB machine operators) add and remove CO_2 through the CPB pump to keep blood pH around 7.4 and P_aCO_2 around 40 mmHg (normal physiologic values). There are however two techniques for acid-base management while on pump: alpha-stat and pH-stat. Alpha-stat management of blood gas values is uncorrected for temperature. This means that blood gases are analyzed at a temperature of 37°C, regardless of the patient's temperature.[1]

[1] In this scenario, the values provided by the blood gas machine will not be the same as the actual values in the patient blood stream, unless the patient is nomothermic. In brief explanation, with decreasing temperature gasses are increasingly soluble. During hypothermia, more of the patient's CO_2 is dissolved in the blood, thus decreasing its partial pressure (i.e. quantity in gas form), termed P_aCO_2. Given that CO_2 is a weak acid, and that the body preferentially wastes H+ ions over bicarbonate ions, an increase in P_aCO_2 results in an extracellular fluid shift to an alkaline pH. When the sample is rewarmed, a higher P_aO_2, P_aCO_2 and a lower pH are recorded than are actually the case in the patient. Further details regarding weak acids are found in Appendix A.

Alpha-stat management in this fashion is believed to preserve intracellular enzyme function, as proteins retain their physiologic charge. In pH-stat management, blood gasses are analyzed at the current patient temperature. Maintaining physiologic values necessitates correcting the fluid back to a neutral pH (at the patient's temperature) by adding carbon dioxide. This increases the CO_2 in the body, increasing vasodilation, increasing cerebral blood flows, and decreasing hemoglobin's affinity for oxygen; all of which may improve oxygen delivery.[38] It remains unclear if manipulating extracellular pH actually modifies outcome in most surgeries, although there is some evidence supporting pH-stat in extended deep hypothermic circulatory arrest.[39] Thus these two acid-base balance management techniques are believed to offer different benefits and risks. The choice of technique may affect intra-operative cerebral cellular injury.

In summary, during pediatric cardiac surgery there are many mechanisms of possible cerebral injury, which are incompletely understood, sometimes poorly identified, and often poorly treated. In an effort to improve upon this state of affairs, and in light of the accumulating evidence previously described concerning neurologic injury and neurodevelopmental delay in this population, a significant interest has developed in identifying critical periods and avoiding injury, inasmuch as is possible.

Intraoperative Neuromonitors

Because of this risk of intraoperative neurological injury, monitoring technologies and devices have been developed in an attempt to identify time periods during surgery when injurious events are likely to be or are actually occurring. The hope behind this work is that when these periods are identified, medical personnel involved in the surgery will be able to adjust or alter the situation in some way so as to avoid or limit patient exposure to injurious experiences. Three such devices, designed to aid in identifying these periods, are quantitative electroencephalogram (qEEG), transcranial Doppler ultrasound (TCD), and near-infrared spectroscopy (NIRS).

Quantitative EEG is a variation on the typical EEG used for monitoring and diagnosing seizure patients. Surface EEGs measure electrical currents transmitted from brain activity via the skull. Generally EEGs are recorded in an amplitude (i.e. surface voltage) versus time plot format. Interpretation of such recordings is time and skill intensive and, as a result, little real-time analysis is possible. Conversion of the traditional EEG signal into a power spectrum of amplitude versus frequency (or other processing, e.g. the bispectral index, commonly referred to as BIS) has allowed for rapid detection of hemispheric asymmetries and changes in frequency content that accompany either deep anesthesia or cerebral hypoxia in the operating room. For example, Hayashida *et al.* correlated an acute change in the EEG power spectrum with an acute drop in cerebral perfusion. Furthermore, they noted that this occurs frequently during pediatric cardiac surgery.[40] These changes are presumed to be secondary to a mismatch between cerebral oxygen supply (essentially via perfusion) and demand.

The value of alterations in intraoperative management based on continuous quantitative EEG intraoperative monitoring is still unclear. Some studies appear to demonstrate an advantage: One demonstrated a decrease in global deficits post-operatively[41], while another demonstrated both a decrease in post-operative disorientation and diminished hospital stay.[42] Both studies, however, included a small sample size and lacked a control group. Other authors have repeated similar studies and failed to demonstrate the same results.[43] Furthermore, there are few pediatric studies utilizing qEEG, and in one large pediatric study, EEG changes were associated with very few abnormal states identified by other neuromonitors; neither did such changes appear to correlate with post-operative neurodevelopmental impairment.[44] Finally, at very cold temperatures, the EEG tracings go flat, presumably reflecting diminished cerebral activity due to hypothermia. In this state, which is common during pediatric cardiac surgery, the qEEG offers no valuable information. Thus, for a significant period of many such operations, this technique offers no additional information or potential for neuroprotection.

A second neuromonitoring technique is transcranial Doppler ultrasound (TCD), which first found favor in the 1980s. It is a non-invasive form of monitoring, used to measure cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) (before it begins to branch). This is the largest of the basal cerebral arteries, and provides ~70% of the blood flow to a given hemisphere. While TCD offers the ability to monitor the CBFV in the MCA in real time, it does not provide any information about regional blood flow or tissue metabolism. Thus, fluctuations in TCD measurements, such as those noted by Rodriguez et al. in neonates after total circulatory arrest, while interesting, are of uncertain clinical significance.[45] Despite this limitation, TCD has been used in neuromonitoring during cardiac surgery in detection of microscopic and macroscopic emboli. Most recently, Yeh *et al.* described a 27-month-old boy who, while under fibrillatory arrest, sustained an air embolus; the use of standard TCD monitoring equipment allowed for rapid and timely intervention, with good neurological outcome.[46] Thus at the very least, TCD may permit the identification and management of rare but potentially catastrophic events. Furthermore, data indicating poor CBFV collected from TCD has been the motivation behind the decreasing use of deep hypothermic circulatory arrest in favor of low-flow cardiopulmonary bypass,[47] as well as the advent of cold reperfusion, wherein the reperfusion begins before full rewarming. [48] However, cerebral blood flow velocity represents only one side of the supply-demand balance. As a result it is essentially impossible to say if the diminished flows we see on hypothermic bypass meet the diminished demands of the brain.

Near InfraRed Spectroscopy

Physics Principles

A third neurmonitoring technique is transcranial near-infrared cerebral spectroscopy (NIRS), a noninvasive monitoring technique based on the principles of optical spectrophotometry and the mechanics of light waves. In brief, light emitted from any source will travel in a straight line until such time as it is reflected, scattered, or absorbed. Reflectance will occur primarily as a result of light aimed at an angle to a surface, directing the light back towards its source. Scattering decreases with increasing wavelengths, with minimal scatter at 650-1100 nm (near-infrared, NIR). Absorption is determined by the molecular properties of the matter in the trajectory of the light beam.

As a function of these properties, light in the NIR range penetrates human tissue several centimeters. Oxygenated and deoxygenated hemoglobin have distinct and disparate NIR absorption spectra, a fact which is exploited by this technology.[49] Light emitted from one end of the probe (which is placed over the forehead) passes through skin, bone and approximately 10 cc of temporal cerebral cortex, to be received at the other end of the probe. Functionally, NIRS assesses cortical oxygenation through the skull in a regional brain sample. This value reflects tissue-level oxygenation and oxygen imbalance with respect to demand. Different patients have different baselines, and variation in NIRS values are somewhat dependant on probe placement and inter-individual differences in absorption properties. [50,51,52] The acquired NIRS values are therefore most informative in the context of relative change. The method of analysis of NIRS changes in the work presented in this thesis reflects this reality (see methods section).

The Beer Lambert Law is the driving physics principle behind the NIRS technology. It states that as light passes through a substance, such as a solution of a colored compound, it will be absorbed, and the amount of light exiting the other side will be reduced. The relationship between the amount of light entering and exiting depends on the concentration of the compound in solution, the extinction co-efficient (a constant property specific to the compound) and the thickness of the solution. One can then reverse this relationship and, knowing the amount of light entering and exiting the solution, the thickness of the solution, and the compound's extinction co-efficient, determine the relative concentration of the compound. In this application of NIRS, the compounds are oxy- and deoxyhemoglobin, and their relative concentrations determine cerebral oxygen saturation.[53]

Devices

Presently, there are two different machines to measure cerebral saturation. One is the Somanetics INVOS; it is the only one which is FDA approved. It functions on the principles outlined above, and is the system used in the research presented herein. In this system, at the receiving end of the probe lie two receptors. The proximal one determines the light absorbed by the extracranial tissue, and the distal determines the total signal.

The difference between the signals received by the two receptors represents the NIR light absorbed by the intracranial tissue. The value displayed by the device is the ratio between oxygenated and deoxygenated hemoglobin, and ranges from 15-95%.

The other available machine is the Hamamatsu NIRO 500. This machine is based on spatially resolved spectrophotometry, and calculates absolute concentrations of oxyhemoglobin and deoxyhemoglobin. This could theoretically lead to increased accuracy and precision of measurement. However, the NIRO lacks FDA approval for clinical use, and does not incorporate a correction for extracerebral tissue oxygenation. The manufacturer claims that the machine also has the capacity to assess the intracellular redox state of mitochondria by examining the NIR absorption of copper atoms in cytochrome a,a3, a marker of intracellular hypoxia. However, when considering that the absorption of near-infrared wavelengths of hemoglobin is significantly larger than that of cytochrome a,a3, and that the latter is dependent on hematocrit (the blood concentration of hemoglobin), it is unreasonable to expect any machine to have a sufficient degree of specificity and sensitivity to be able to detect these intracellular changes reliably. At least one study has attempted to explore the validity of the cytochrome signal, and determined it to be highly dependent on hematocrit.[54]

Attempts have been made to compare the two devices.[55,56,57] In one study[58], subjects inhaled either 7% CO_2 in O_2 or 10% O_2, inducing hypercarbia and hypoxia, respectively. The investigators found that while both devices demonstrated appropriate increases in values with hypercarbia and decreases in values with hypoxia, the absolute values recorded by the NIRO 500 tended to be greater than those recorded by the INVOS 3100A. They hypothesized this difference to be due to the lack of correction for skin and bone absorption in the NIRO 500. However, a major problem with this study is the small sample size (5 subjects) and the fact that each device was recording only unilaterally. As we will see in subsequent sections, different hemispheres may have differing directions and degrees of responses to the same systemic variation. The study results could be significantly affected by a single such patient. Bland and Altman compared the two devices, showing that while correlation between monitors was good in large samples when examining changes in NIRS values from baselines (r = 0.85), correlation for individual values was lower (r = 0.58). [59]

NIRS values as an outcome variable

In an attempt to understand NIRS monitoring, a variety of studies have been conducted in order to determine which physiologic variables are correlated with NIRS values and events. NIRS is supposed to measure cerebral cellular oxygen tension, which is determined by oxygen supply and use. Oxygen supply is determined mainly by oxygen carrying capacity of the blood and blood delivery (perfusion) to the brain. Oxygen use is determined by cerebral cellular demand. Thus, the literature on NIRS tends to fall into one of these three categories (correlation with oxygen carrying capacity, correlation with perfusion, or correlation with demand). Furthermore, while there have been some experiments in animals, the majority of the evidence arises from observational, human studies.

In this section, we will review the published literature, beginning with papers addressing the correlation of NIRS to measures of oxygen carrying capacity. Following that, we will review the literature examining the relationship between NIRS and blood delivery or perfusion. Finally, we will review the published work assessing the relationship between NIRS and factors affecting oxygen demand. We will then proceed to the subsequent section of the introduction, assessing the clinical correlates of NIRS changes.

Measures of oxygen carrying capacity and NIRS

Much of the literature focuses on the correlation between measures of oxygen carrying capacity and NIRS. As background, it is important to note that blood carries oxygen in two ways: dissolved in the plasma, and attached to hemoglobin molecules in red blood cells. The latter is far more efficient and more important to oxygen delivery. Thus in any attempt to analyze the quantity of oxygen being delivered per unit of blood, one must consider arterial oxygen content, hemoglobin concentration and saturation levels. A fourth quantity of interest is the venous oxygen content which reflects the amount of oxygen which has been removed from the blood, presumably by active cells.

Subsequently, in order to understand NIRS as a measure of cerebral oxygen tension, authors have attempted to demonstrate a correlation between NIRS measures and venous saturation (mixed, central and/or jugular), arterial oxygen saturation, and hematocrit (hemoglobin concentration). Hemoglobin saturation with oxygen can be assumed to be near 100% in arterial blood.

Venous oxygen saturation is clinically measured in different locations: jugular, mixed venous, and central venous. There is conflicting data on the relationship between venous oxygen saturations and NIRS values. Some studies have found evidence supporting a significant correlation between NIRS and central venous oxygen saturation[60,61] or jugular venous oxygen saturation[62, 61]. Daubeney's group, for example, compared cerebral saturations as measured by NIRS to jugular venous saturations and found a good correlation in those less than a year old ($r^2 = 0.85$) and a significant, albeit weaker correlation in those aged 1 year and over ($r^2 = 0.57$).[63] Tortoriello's group demonstrated a moderate correlation between central venous oxygen saturations in a group of post-operative pediatric cardiac surgery patients and NIRS.[64]

More than one group, on the other hand, showed that NIRS failed to correlate with jugular venous oxygen saturations.[65,66] Another study showed (using the Bland-Altman method of analysis) that the NIRS device sensitivity to detect low venous oxygen saturations was quite poor (46%).[67] In this study, the degree of correlation was shown to be dependent on the precise site of the tip of the central venous catheter, being highest when in the inferior vena cava (r=0.814), followed by the superior vena cava (r=0.640), with the right atrium being a distant third (r=0.284). These differences could account for some of variability in the published literature.

In examining the relationship between arterial oxygen saturations and NIRS values, several authors were unable to demonstrate a correlation[68,69]. Several authors however did demonstrate a correlation with arterial saturations[70,71,72]. The reason for the difference may be that those demonstrating a correlation may have had greater range of arterial saturations, allowing a significant correlation to be easier to confirm.

Similarly, researchers proceeded to try to define the precise relationship between arterial and venous oxygen contents and cerebral oxygen saturation. They asked: What component of the NIRS reading is arterial, and what component is venous? Previous studies had used a weighted average of arterial and jugular saturations in a 25:75 ratio[73, 74, 75]. However, one paper[76] showed that the arterial and venous contributions were 16 +/- 21% and 84 +/- 21% respectively, which may partially account for some of the discrepancies in published conclusions.

The final consideration in blood oxygen carrying capacity is hemoglobin concentration or hematocrit. Hemodilution decreases oxygen delivery; normally this is partially compensated by increased cerebral blood flow due to cardiac output (unavailable while on CPB), cerebral vasodilation and/or decreased viscosity.[77] Various studies included red blood cell measures in their analyses, but failed to demonstrate any conclusive relationship, possibly due to a lack of variability in hemoglobin, or a lack of power. [78] Others successfully demonstrated a relationship.[79,80] In a series of piglet models, NIRS signals were significantly lower when an alpha-stat strategy was combined with hemodilution. NIRS signals dropped more rapidly, regardless of strategy, in hemodiluted patients.[81] In the second study, a higher cerebral blood flow and metabolic rate of oxygen was associated with a lower hematocrit.[82] In the third relevant study, the authors demonstrated that a shorter time to a nadir value of NIRS was associated with lower hematocrit levels.

Perfusion/Delivery

It is evident that blood oxygen content is unimportant if none or little of the blood reaches the brain cells. In an attempt to further understand the spectroscopy instrument, authors have examined the degree to which variables affecting perfusion affect NIRS. It is important to take a moment here to discuss cerebral perfusion, as it is determined by several physiologic principles. First and foremost, as with any organ, perfusion is dependent on arterial pressure. However, the brain has the ability to autoregulate, which complicates the relationship somewhat. In healthy, normal populations, within non-extreme ranges of physiologic values, the brain autoregulates to control cerebral perfusion pressure (CPP). This prevents excessive flow in mildly hypertensive states, and guarantees sufficient flow in mildly hypotensive states.[83]

Generally speaking, the brain requires about 15% of the total cardiac output and a minimum mean arterial pressure (MAP) to satisfy cellular metabolic demands. Furthermore, unlike the rest of the body, the brain has little to no reserves of glucose, and requires this perfusion on a continuous basis. While dependent on a minimum arterial pressure in order to provide sufficient cerebral blood flow, optimal regional cerebral blood flow is maintained by the cerebral vasculature which vasodilates and vasoconstricts in response to various physiological conditions. This autoregulation can be maintained so long as MAP is maintained within 0.75 to 2 times normal MAP. Beyond these ranges, cerebral blood flow varies linearly with MAP.[84]

Other factors affecting cerebral blood flow include partial pressures of carbon dioxide and oxygen. Within a wide range of P_aCO_2 values (20-50 mmHg), cerebral blood flow is almost linearly related thereto. The vasoconstriction seen with extreme changes in P_aCO_2 (i.e. less than 20 mmHg) may produce local ischemia and hypoxia. The cerebral vascular resistance also seems to vary inversely with P_aO_2, providing more flow when concentrations of oxygen are lower.[85]

Thus, we expect that in normal states, or mild-moderate deviations from such, the brain will autoregulate in order to provide sufficient oxygen to meet cerebral demands, without exceeding them. However, we also know that this autoregulation fails, and cerebral blood flow becomes linearly related to MAP, at CO_2 levels above 50 mmHg.[86] The implication of this is that with CO_2 levels greater than 50 mmHg, as is often seen with pH-stat management, the brain experiences excessive perfusion with only borderline high MAPs, and insufficient perfusion with slightly low MAPs.

Several studies have attempted to examine the effect of perfusion or determinants of cerebral blood flow velocity (CBFV), on NIRS values. If NIRS were a valid measure of cerebral perfusion, we would expect to see stable values across normal ranges of MAP, with NIRS values increasing with MAP in the context of high P_aCO_2 levels, in normal patients. However, children with congenital cardiac disease are at high risk for cerebral autoregulation dysfunction and are likely to manifest variability even within normal P_aCO_2 levels.[87]

In 2005, Bassan et al examined the relationship between NIRS values and CBFV in infants.[88] As expected, they found a correlation between NIRS and CBFV. They further found a significant relationship between MAP and NIRS, suggesting a failure of cerebral autoregulation, as discussed above. Finally, they noted a correlation between NIRS measurements and P_aCO_2, with increased likelihood of pressure passive circulation (loss of autoregulation) at P_aCO_2 levels > 40mmHg. Another author noted a similar loss of autoregulation, with a clear relationship between MAP and NIRS measurements, particularly in the younger age groups.[89] Other authors have also noted a similar relationship between NIRS and P_aCO_2.[90,91]

Importantly, another series of studies has confirmed that, when on CPB, MAP is determined by pump flow (and systemic resistance) and that blood flow is different than it is naturally. These authors have examined the relationship between CPB machine flow and NIRS. One study failed to notice any difference between pulsatile and non-pulsatile flow.[92] Another failed to find a correlation between pump flows and NIRS measures, but recognized that the variability across the former may have limited their ability to uncover any existing relationship.[93] It is also important to acknowledge the possible conclusion that NIRS simply doesn't reflect cerebral blood flow well.

Demand

The final important determinant of cerebral cellular oxygen supply-demand ratio is the demand component. During cardiac surgery, cerebral demand is less than normal. This is in part due to the anesthetic depth. Hypothermia is also deliberately induced, to lessen demands, with circulating blood being cooled, and ice packs being placed on the head. It stands to reason that if NIRS were a valid measure of the supply-demand ratio, measured values would correlate inversely with cellular demand.

Barring invasively measuring cerebral enzymatic status, all measures of demand must be indirect. Furthermore, measuring brain activity on EEG would be suboptimal, as we would expect to see a deficiency in relative oxygen supply precede any electrical changes. Thus published works have focused on the easily measured parameter of temperature. Nollert et al. observed that NIRS would fall less at lower body temperatures than at higher body temperatures.[94] Lassnig et al concurred.[95]

Finally, one study examined non-cerebral tissue perfusion, and found that NIRS compared favorably with an invasive measure of oxygen supply-demand balance.[96]

NIRS as a predictor variable (for CNS or other outcome)

The aforementioned work offers some face and construct validity support for NIRS as a measure of cerebral tissue oxygen saturation, by demonstrating some consistency with factors affecting cerebral oxygen delivery and demand. Predictive validity, which relates more to the question of medical utility or patient benefit, however, has not yet been substantially addressed, at least in pediatric populations.

Studies on animal populations have explored various neurocognitive outcomes. Kurth et al demonstrated that decreasing NIRS values correlated with worsening EEG changes, and ultimately decreased brain ATP.[97] Sakamoto et al demonstrated that low NIRS values correlated with poor histological outcomes, as well as poor clinical outcomes.[53,80] Taga and Nollert both demonstrated, using MR-spectroscopy, that low NIRS values were associated with decreased ATP levels.[98,99] In a human neonatal population, Dent et al. demonstrated that prolonged low intraoperative cerebral saturations were associated with the worsening of existing ischemic lesions, and the development of new such lesions.[100] Thus, a variety of deleterious histological, radiological and clinical outcomes have been correlated with low NIRS values. Of note, none of these studies addressed the issue of whether responding to NIRS values intraoperatively affected outcomes.

Several authors have examined the utility of responding to NIRS values in human populations, using differing clinical outcomes. Hoffman et al examined the effect of NIRS on the development and severity of shock, using base excess as an indirect marker thereof.[101] They found that incorporating NIRS technology into their PICU with treatment of low values resulted in a decreased number of events (significant changes in base excess) and thus fewer episodes of biochemical shock. The control in this study was historical, with statistical methods demonstrating a trend over time.[102] Yao et al examined the effect of introducing intraoperative NIRS (with a predefined reaction algorithm) on length of stay in the ICU and in the hospital, in an adult population. Despite being a prospective study, again, a non-contemporaneous control cohort was used.[103] Austin et al performed a similar study, the results of which were reported in the landmark paper on neuromonitoring in a pediatric population undergoing cardiac surgery.[104] In this retrospective study of 250 patients, the authors found that 70% of patients experienced cerebral ischemia/hypoxia as identified by NIRS, TCD or EEG. Of this 70%, 74% were intervened upon intraoperatively. In addition to neurological outcomes (discussed below), the authors examined length of stay in hospital. They found that those patients who had manifested no events or had had their events "treated" had a three day shorter length of stay, than those patients who experienced events to which there was no reaction. In a small twist, Fenton et al examined the correlation between baseline (pre-operative) NIRS values and mortality in a pediatric population undergoing congenital heart surgery. They found an increased mortality amongst those patients with a low preoperative cerebral saturation.[105]

A few studies have also examined neurological and neurocognitive outcomes. Toet et al followed 20 infants and looked at the relationship between perioperative NIRS values and neurocognitive assessments performed at 30 months post-operatively.[106] They found that patients with lower preoperative cerebral oximetry readings had lower developmental quotients at follow-up. Kurth et al, studied 12 children and infants undergoing cardiac surgery and found that the three patients who sustained adverse neurocognitive outcomes post-operatively had sustained lower intraoperative cerebral NIRS.[107] Austin et al, in the aforementioned study[108], noted that the rate of neurological complication (seizure, movement, vision or speech disorder) was nearly identical in the group that did not experience a neuromonitoring event and the group that did, but received intervention (6 and 7% respectively); furthermore, this rate was nearly five-fold lower than that seen in the non-intervention group (26%). This retrospective, non-randomized study is the best current evidence for NIRS use intraoperatively in children. The report is vague on why the non-intervention group did not receive any intervention, and characteristics of the two groups are not examined for potential confounding.

The literature supporting the use of NIRS in adults is more extensive. Casati et al published a prospective, observational study wherein they showed that in elderly patients undergoing major abdominal surgery, the desaturations seen on cerebral oximetry were correlated with longer hospital stays and higher rates of postoperative cognitive dysfunction as measured by the Mini Mental Status Exam.[109] Goldman's group used a historical control to evaluate the effect of addition of intra-operative NIRS on post-operative stroke rates, and found a significant reduction.[110] Iglesias et al., in a randomized controlled study, demonstrated that adults undergoing cardiac bypass grafting with NIRS monitoring and reactions thereto to maintain NIRS > 75% of baseline had a decreased length of stay in hospital.[111]

In summary, NIRS has been studied by many authors, in many circumstances, and there is sufficient evidence to lend credibility to it having a positive impact on intraoperative events and ultimate outcome. However, there is little evidence that the monitor and response algorithms have systematically altered pediatric outcomes in any meaningful fashion.

Thesis work

The body of this thesis consists of three manuscripts. These studies were performed to expand our knowledge of the potential utility of neuromonitoring in a pediatric population undergoing cardiac surgery. The first paper describes a study examining the correlation of key hemodynamic and respiratory variables with significant decreases in NIRS readings, in an attempt to determine potentially modifiable variables contributing to said decreases. The second paper examines a previously undescribed facet of NIRS, i.e. significant increases in NIRS values. We describe the frequency, duration and timing of these two sets of events, and assess various hemodynamic and respiratory correlations. The third paper explores the aspect of bilateral monitoring, to establish a context for future work, as up to present there has been much variation in published work. The papers vary slightly in format, due to anticipated journal requirements for submission.

In addition to these papers, the expanded description of the methodology and the discussion will deal with issues pertinent to the field of epidemiology, including the patient selection process; the data gathering method; outcome measures; and analysis. The process of data analysis will also be reviewed in greater detail, with expanded interpretations of what the results may imply.

Contributions of Authors

The bulk of the manuscripts, including study design, data collection, data analysis, and manuscript preparation was performed by Samantha Hill. All other authors contributed in a meaningful fashion to study design and manuscript preparation.

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Methods

Study design:

All three papers are based on a case series design, wherein each subject serves as their own control.

Study population:

All patients, of all ages, undergoing open heart surgery at a single center (Montreal Children's Hospital) with a single surgeon (CT) were candidates. Inclusion criteria included the operative procedure requiring cardiopulmonary bypass and the surgery occurring between August 23, 2005 and April 20, 2006. Exclusion was limited to those cases for which the data collector (SH) was unavailable. This represented less than 1% of the eligible population.

The first two papers studied an identical population. This sample included 32 males (64%) and 18 females (36%). Twenty-seven (54%) were cyanotic. For individual diagnoses, please see the papers. Further demographic data can be found in the table below.

CHARACTERISTIC	MEDIAN	MEAN	RANGE
Age of Full Sample	165 days	833 days	[1,3869]
Neonate (0 to 30 days)	9 days	12 days	[0, 27]
Infant (31 to 365 days)	128 days	134 days	[43, 265]
Child (>1 year old)	1676 days	1954 days	[382, 3869]
Body Surface Area	0.35	0.50	[0.22, 1.32]
Baseline NIRS	70	65.5	[30, 86]

The third paper studied a population of 65 patients which subsumed that previously described. In this slightly larger population there were 41 (63%) males and 24 (37%) females. Forty (62%) of these patients were cyanotic. The ages were evenly distributed across three strata: 20 neonates, 22 infants and 23 children. Baseline NIRS values ranged from 30 to 91, with the average baseline being 66.

Sample size calculation:

A rule of thumb often used for logistic regression is 10:1, i.e. ten patients for each independent variable[1]. Using this rule, to assess 7 variables a minimum of 70 patients are desirable. With this in mind, analyses were run on the 50 patients for whom complete data had been collected, and we limited ourselves to the five predictor variables we felt were most likely to be important.

Variables and their measurement:

Demographic data were extracted from electronic and paper-based hospital records. These included date of birth, date of surgery, gender, anatomic lesion and body surface area. Potential independent predictor variables were collected via inline cooximetry (gas partial pressure measures) and flow rate readings on the cardiopulmonary bypass machine, invasive arterial blood pressure measurement, and nasopharyngeal thermometer. All variables were continuous. Each of these measures is considered to be the gold standard for the respective phenomenon. The primary outcome variable was based on NIRS measurements. Events, as defined below, were identified.

Raw NIRS data were collected throughout the surgery and situated with respect to the following time periods: before circulation was supported by CPB, at institution of CPB, during cooling, at aortic cross-clamp application, at aortic cross-clamp removal, during rewarming, at the time of transition of the circulation back to the patient and after circulation was resumed by the patient. Three sets of data were collected for each event, with measurements recorded 1) just prior to a deviation from baseline, 2) at, or just prior to, the nadir/apex of a NIRS deviation from baseline and 3) at the time of return to baseline. Duration of a change from baseline and percent change were recorded and calculated respectively. At each of these times, seven variables were recorded:

- pH: a measure of the acid-base status of blood
- p_aO_2: the partial pressure of oxygen dissolved in the blood
- p_aCO_2: the partial pressure of carbon dioxide dissolved in the blood
- Hct: hematocrit, a measure of hemoglobin concentration
- Temp: nasopharyngeal temperature
- MAP: mean arterial pressure
- iCPB: cardiopulmonary bypass pump flow indexed to body surface area

Definition of the outcome variable:

In keeping with previously published work, downward deviations of 20% or greater from baseline NIRS values (established preoperatively) were considered significant events[2,3]. In the work presented here, we extrapolated this, by simple analogy, to increases as well as decreases. The outcome variable was dichotomous: presence or absence of an event. Control periods, or absence of an event, were defined as the first return to within 20% of baseline. For the purpose of the first two studies, events lasting less than 15 seconds, which are unlikely to be physiologically important, were excluded. For the third study, we required a duration of 2 minutes, as in our opinion, in the context of a presumed intact circle of Willis, unilateral deviations of less than 2 minutes likely pose little clinical relevance.[4]

Data collection methods:

Demographic data such as date of birth, anatomic lesion and gender were obtained from chart review at the time of surgery.

For the studies described in the first two papers, event data were extracted to a standardized form by the first author using a combination of intraoperative records and real-time values. An example of this form can be found in Appendix B.

For the study described in the third paper, the intraoperative data collection was a little different in that continuous data was collected by the NIRS monitor when activated. This data is stored as a summary value in 10-second intervals. Thus every 10 seconds, the monitor saves a line of data with the time and the algebraic means of left and right sided NIRS values over the preceding 10 seconds. This data is stored and displayed in an Excel file. Data in this file were used in subsequent analyses.

<u>Data validity/reliability:</u>

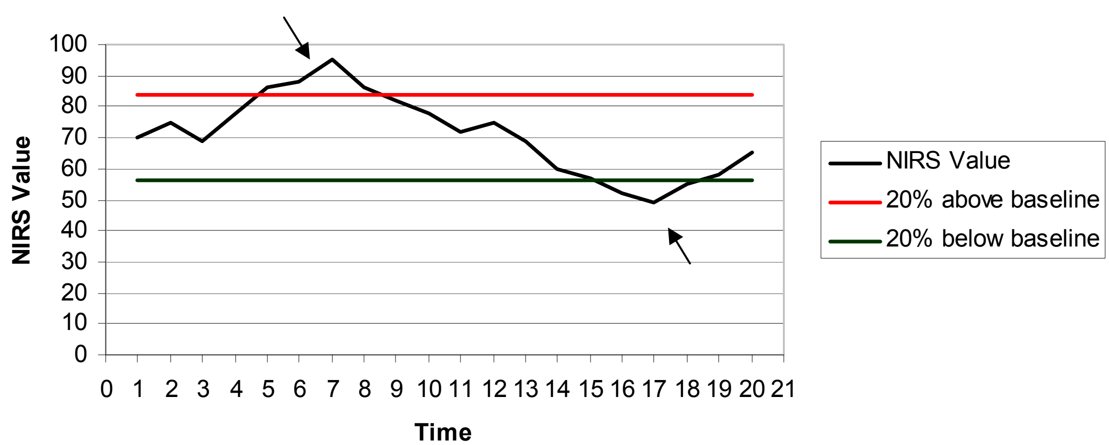
With respect to the first two studies, approximately 10% of cases were re-coded at a later time by the first author (SH), blinded to the initial coding, to assess reliability of the coding. No discrepancies were identified in event identification or description. The validity of the monitor-collected data was not assessed in these studies, although they have been previously examined by the manufacturer with good inter-observer validity (personal communication) and inter-test validity[5].

<u>Data organization:</u>

For the purpose of analysis for the first two papers, the data were extracted and reorganized so that NIRS was assigned a binary value. The value 1 represented an event; the value 0 represented a control portion, i.e. identification of a return to baseline. The variables, corresponding to the parameters described in the "Variables and their measurement" section, were collected at three times: preceding the event, at the apex/nadir of the event, and upon return to baseline. The variables were then reorganized to establish two "sets" of data. For NIRS = 1, the variables were calculated such that each represents the difference between baseline and nadir/apex values. This represents the changes in said variables as an event was occurring. For NIRS = 0, the variables were calculated as the difference between values at the time of baseline and upon return to baseline. This represents the changes in said variables between two periods without an event, or two baseline periods. This design was chosen in order to adjust for differences in baseline NIRS values between individual patients.

For heuristic purposes, consider the following scenario (Figure 1). In a sample patient, the NIRS value at time 1 is 70. This value of 70 would represent the baseline. 20% above this baseline is 84, denoted by the upper horizontal line. 20% below the baseline is 56, denoted by the lowerr horizontal line. So long as NIRS value ranges between 56 and 84, there are no significant 'events'. But, the diagram includes arrrows. The first arrow is located at the apex of a significant positive deviation from baseline, the second at the nadir of a significant negative deviation from baseline. For the first event, the last time that the NIRS value is within 20% of baseline is at time 4. The apex occurs at time 7, and the return to within 20% of baseline occurs at time 9. If we take hematocrit as an example, for NIRS = 1 the hematocrit variable would equal the difference between the hematocrit values at time 7 and at time 4. For NIRS = 0, the hematocrit variable would equal the difference between the values at time 9 and at time 4. The same process would be repeated at time 17, using times 15 and 19 for baseline values.

Figure 1: Sample Patient



Thus the dependent variable is categorical, corresponding to the presence (1) or absence (0) of a significant change from baseline. All independent variables are continuous, corresponding to a change in hemodynamic and gas exchange parameters from baseline.

Because two of these variables change in one hundredths of units (hematocrit and iCPB), these were multiplied by 100 to give the odds ratios practical meanings.

For the third paper, no data transformation was undertaken.

Statistical software:

All calculations for the first two papers were performed using SAS 9.0. For the third paper, statistical analyses used Excel 2000, and SISA, an online rate ratios comparison software (home.clara.net/sisa).

Descriptive statistics:

Descriptive analyses were performed to assess the number of observations and explore the issue of any missing data. Outliers were identified, reviewed, and corrected when found to be incorrectly entered into the original database. For the first two papers presented here, the values of all variables were further examined to ensure that the data collected during events was in a comparable range, with comparable variances, to that collected when the NIRS were within 20% baseline. Although not required for binary logistic regression, the data was assessed and normality was assured both prior to and subsequent to imputation, the latter via assignation of zero to all missing values.

Missing values:

In the first two papers, there were a significant, although not unexpected, number of values missing (See "Results" section). In order to place the burden of proof on the alternative hypothesis of no significant correlation, an assumption was made that all missing values were equal to zero. That is, any value for which there was no data has been imputed to have had no difference between the two time periods, and would not account for the variance in dependent variable. In order to check this assumption a series of analyses were performed including comparing histograms, and sequential univariate analyses. No significant differences were found amongst the mean, nor the distribution, of the independent variables after imputation. Furthermore, the conclusions of the regression models were not altered. In the third paper, missing values were not as frequent. When present, we excluded these time periods' data from the analysis.

<u>Data analysis:</u>

In the third paper, proportions were compared using a two-sided Student's T-test. Rate ratios were compared using SISA's usual Chi-square distribution to calculate the exact Poisson confidence interval.

For the first two papers, the process was slightly more complex. Univariate models for each of the independent variables were assessed. A series of simple logistic regressions between independent variables and the dependent variable were fitted to the data. These were followed by multivariate models with each variable and its quadratic terms. Quadratic terms were included in the multivariate model when they improved the model fit. Using the independent variables in either linear or quadratic form, logistic regression was used to model the relationship with NIRS deviations from baseline.

In general, no adjustment was made for the possible non-independence of multiple events in a single patient. This approach was chosen as we felt that the underlying relationship between independent variables and NIRS measurements were primarily driven by intrinsic physiologic principles and not characteristics of individual subjects. We recognize that had an adjustment for possible non-independence been included it may have diminished the level of significance of certain independent variables.

Correlation matrix

For the first two papers, a correlation matrix was assessed amongst the independent variables. There were no significant correlations leading to variable exclusion from the final model.

Possible confounders/effect modifiers

Interaction terms including variables known to be related a priori were assessed; ultimately these did not prove necessary for inclusion in the final model as they did not explain significant variance.

Model selection procedures:

The final model was selected based on a combination of AIC (Akaike Information Criterion) and clinical relevance. Several automated models were applied to the data, including backward, forward, and stepwise procedures. This process was repeated on the data set with missing data not imputed to be zero, with no resulting difference in model selection. Finally, the data was split in two and cross-validated, with no change in final model selection.

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Manuscript One: One, Two, Three Strikes – You're Out! Near Infrared Spectroscopy Event Predictors

Thus far in this thesis we have reviewed the literature currently published on the subject of NIRS, and demonstrated a significant lack of knowledge in the field of paediatrics. Furthermore, we have explored various physiologic variables that have been found to be associated with NIRS values in predominantly animal models. The Methods section has elaborated on details not included in the manuscripts.

The first manuscript: "One, Two, Three Strikes -- You're Out! Near Infrared Spectroscopy Event Predictors" is the first of three presented in this thesis. The goal of this paper was to attempt to provide information regarding the behaviour of NIRS in a paediatric population undergoing open heart surgery requiring CPB, and to further understand those low events commonly accepted to be potentially deleterious. The definition of a significantly low value was consistent with that in the published literature, and the physiologic variables have all been discussed at length. This is the first manuscript presented as it concerns issues the most similar to previously published work, however it contributes to the current body of literature both as a result of the pediatric patient population and as it utilized a human model.

Manuscript 1: One, Two, Three Strikes -- You're Out! Near Infrared Spectroscopy Event Predictors

Hill SJ, Lavoie J, Rohlicek C, Dougherty G, Tchervenkov C

Abstract

Background: *The decreasing mortality from congenital cardiac surgery has permitted increased recognition of associated morbidity, particularly neurological impairment. The use of Near Infra-Red Spectroscopy (NIRS) and other intra-operative neuromonitoring techniques may improve neurological outcomes (1). Independent variables have been identified in animal studies (2).* ***Objective:*** *We hypothesized that significant decreases in NIRS values during congenital cardiac surgery involving cardiopulmonary bypass were associated with basic intraoperative physiologic parameters.* ***Methods****: In 50 consecutive bypass pediatric congenital cardiac cases, data on seven continuous independent variables (pH, P_aCO_2, P_aO_2, hematocrit, temperature, mean arterial pressure (MAP), and indexed pump flow) were collected. Simple and multivariable univariate logistic regression were used to model the outcome variable (i.e. a 20% decline from NIRS baseline value).* ***Results:*** *The population included 12 neonates (0 to 30 days old), 17 infants (31 to 365 days old), and 21 children (366 days to 18 years old). 82% manifested at least one monitoring event, ranging in duration from 0.5 to 40 minutes (mean 11.9). More events occurred when circulatory support via cardiopulmonary bypass was commenced than during any other intraoperative period. In univariate analyses, only three variables were found to be significantly associated with NIRS decreases: P_aO_2 ($p = 0.0005$), hematocrit ($p < 0.001$), and MAP ($p < 0.001$). On multiple univariate logistic modeling, the same three variables were statistically significant ($p<0.05$). In this model, the coefficients were: P_aO_2 0.02 (95% CI [0.008, 0.021]); hematocrit 0.59 (95% CI [0.28, 0.90]); and MAP 0.19 (95% CI [0.092, 0.288]). A decrease of 10 torr in P_aO_2 was associated with an odds ratio (for NIRS decline) of 1.22. A 3% absolute decrease in hematocrit was associated with an odds ratio of 5.83. A decrease by 5 mmHg in blood pressure was associated with an odds ratio of 2.59.* ***Conclusion****: Significant decreases in NIRS are consistently associated with hemodynamic/respiratory parameters, and often occurred when going on pump. NIRS*

may play a role in intra-operative cerebral protection by guiding hemodynamic and respiratory management.

Background

Light in the near infrared range penetrates human tissue several centimetres, and is absorbed by tissue to varying degrees. Oxyhemoglobin and deoxyhemoglobin have different NIR absorption spectra.[1] Based on this differential absorption, transcranial near-infrared cerebral spectroscopy (NIRS) assesses cortical oxygenation through the skull in a regional brain sample (rSO_2). This value seems to correlate with an 85:15 ratio of arterial:venous blood SO_2[2], and is taken to reflect tissue-level oxygenation and oxygen imbalance with respect to demand. Since different patients have different baselines, the acquired rSO_2 level is most informative in the context of relative change.

Transcranial near-infrared cerebral oximetry has become increasingly accepted as a valuable method of neurophysiologic monitoring. Substantial retrospective data has been accumulated which appears to demonstrate promising results. Harris and Bailey demonstrated an association between low values measured and adverse outcomes post-cardiac surgery.[3] Austin et al. noted that interventions based on neurophysiologic data accumulated intra-operatively on pediatric patients decreased the incidence of post-operative neurological adverse events, decreased length of hospital stay, and appeared to be cost-effective to the institution.[4] Iglesias et al., in a randomized controlled study, demonstrated that adults undergoing cardiac bypass grafting with NIRS monitoring and reactions thereto to maintain $rSO_2 > 75\%$ of baseline had a decreased length of stay in hospital.[5]

Despite the evidence, there remains doubt concerning the use of NIRS in a pediatric cardiac population. In an attempt to further understand NIRS monitoring, a variety of studies have been conducted. For the most part, in these studies, physiologic variables are correlated with NIRS values and events. NIRS is supposed to measure cerebral cellular oxygen tension, which is determined mainly by three criteria: oxygen carrying capacity of the blood, delivery (perfusion) to the brain, and cerebral cellular demand.

Thus, the studies tend to fall into one of these three categories. While there have been some experiments, in animals, the majority of the evidence arises from observational, human, studies. Importantly, much of the published evidence gives apparently conflicting results.

Daubeney's group compared cerebral saturation as measured by NIRS to venous saturations returning from the brain via jugular bulb oximetry. They found a good correlation in those less than a year old ($r^2 = 0.85$) and a significant, albeit weaker correlation in those aged 1 year and over ($r^2 = 0.57$).[6] Harrris' group, on the other hand, showed that NIRS failed to correlate with jugular venous oxygen saturations.[7]) Other studies continued the debate.[8,9]

NIRS signals have been shown to drop more rapidly in hemodiluted piglets.[10] Yet, in another (adult) study, in a multiple linear regression model, hematocrit was not an independent predictor variable.[11] A third (pediatric) prospective study demonstrated that the frequency of cerebral ischemia correlated significantly with the mean hematocrit ($r = -0.295$, $p<0.01$ on multiple linear regression (MLR); $r = 0.469$, $p<0.0001$ on simple linear regression (SLR)).[12]

One clearly reproducible correlation has been described. In 2005, Bassan et al. found a correlation between NIRS and cerebral blood flow velocity (CBFV). They further found a significant relationship between NIRS and mean arterial pressure (MAP), demonstrating a failure of cerebral autoregulation. Finally, they noted a correlation between NIRS measurements and P_aCO_2, with increased likelihood of pressure passive circulation (loss of autoregulation) at P_aCO_2 levels > 40mmHg. Another author noted a similar loss of autoregulation, with a clear relationship between MAP and NIRS measurements, particularly in the younger age groups.[13] Other authors have noted a similar relationship between NIRS and P_aCO_2.[14,15]

Another series of studies has acknowledged that, when circulatory support is provided by CPB, MAP is determined by pump flow (and systemic resistance) and that blood flow is different than it is naturally. These authors examined the relationship between CPB machine flow and NIRS. One study failed to notice any difference between pulsatile and non-pulsatile flow.[16] Another failed to find a correlation between pump flows and NIRS measures, but admitted that the variability across the former may have limited their ability to uncover any existing relationship.[17]

Few studies have examined the role of temperature, which would affect metabolic demand, on NIRS. Nollert et al. observed that NIRS would fall less at lower body temperatures, than at higher body temperatures[18]. Lassnig et al concurred.[19]

Objectives

This study had two objectives. The primary objective was to describe the behavior of NIRS in a congenital cardiac population, with attention to frequency and duration of low-value events, as well as identifying the highest risk periods for significant NIRS declines. The secondary objective was to characterize these events as indicators of cerebral hypoxia, by identifying correlates of these events.

Methods

Cerebral near infrared spectroscopy was measured bilaterally. The forehead was cleaned using the acetone/alcohol preparatory pads provided, and allowed to dry. Pediatric sensors were placed over bilateral fronto-temporal regions. These sensors were trimmed as necessary to allow bilateral placements. In these cases, light-occluding tape was placed over the junction of the two sensors. Baseline NIRS measurements were established in patients while awake and calm, unless the patient was hemodynamically unstable. NIRS data were measured using the Somanetics INVOS 5000, which also records all collected data, at a rate of one measurement per 30 seconds. These data were recorded for each patient in a spread sheet, an example of which can be found in Appendix B.

Physiologic data was measured continuously. In-line oximetry provided pH, P_aCO_2, P_aO_2, and hematocrit. Afferent blood temperature, and pump flow were read directly off the cardiopulmonary bypass machine. Pump flow was later indexed to body surface area. Patient temperature was measure by a nasopharyngeal thermometric probe.

The intraoperative data of 50 consecutive pediatric cases undergoing congenital cardiac surgery requiring cardiopulmonary bypass were reviewed. Significant decreases of NIRS values, defined as 20% below the patients' baselines, were identified.[20]

Descriptive data were summarized using means with standard deviations, or proportions, as appropriate. Differences were tested using basic statistical tests, such as the Student's t-test or the chi-square test. Using simple and multiple logistic regression models, differences from baselines in all independent variables were compared at times of low NIRS values with those at time of recovered NIRS values.[1] Each patient thus provided their own control data. When data were not available, values of zero were imputed in order to put the emphasis on disproving the null hypothesis. All statistical analyses were done using SAS software. We required a level of significance of $p < 0.05$.

Results are expressed in terms of odds ratios with 95% confidence intervals. Odds ratios describe the difference in the odds of a low NIRS value occurring with a 1 unit change compared to baseline in the dependent variable: a change in Δp_aCO_2 or Δp_aO_2 of 1 torr; a change in Δtemperature of 1 degree Celsius; a change in ΔMAP of 1 mmHg; a change in Δindexed pump flow of 1 $l/min*m^2$. However, because pH and hct vary in one hundredths of units (i.e. 7.40 to 7.39, and 0.32 to 0.31 respectively) these were multiplied by 100 to give the odds ratios practical meanings. Thus the OR for the change in ΔpH and Δhct variables represent the difference in odds of a low NIRS occurring when pH or changes by 0.01 unit. I.e. from 7.40 to 7.39 or from 32% to 33%.

Results

<u>Population</u>

This cohort of 50 children included 12 neonates (30 days or less), 17 infants (31 to 365 days), and 21 children (older than 1 year). Ages ranged from 1 to 3869 days (10 years, 7

[1] See Figure 1 in Methods

months) with the mean being 833 days (2 years, 3 months), and the median being 165 days. The average age in each category was 7 days, 133 days, and 5.2 years respectively. The anatomic diagnoses are listed below. The sample included 32 males (64%) and 18 females (36%). Nine patients (18%) exhibited no significant decreases in rSO_2 throughout the operation and thus did not contribute to the regression models.

Table 1 Subject Diagnoses

DIAGNOSIS	**# OF SUBJECTS**
Tetralogy of Fallot	9
Left Heart Obstruction (Subaortic Stenosis, Aortic Stenosis,)	8
Ventricular and/or Atrial Septal Defect	6
Atrioventricular Septal Defect	6
Pulmonary Valve/Right Ventricular Outflow Tract Obstruction	5
Transposition of the Great Arteries/ Double Outlet Right Ventricle-TGA type	4
Mitral/Tricuspid Valve Pathology	3
Double Inlet Left Ventricle	2
Total Anomalous Pulmonary Venous Connection	2
Other *	5

* Includes one of each: Aortopulmonary Window, Cor Triatriatum, Double Chambered Right Ventricle, Truncus Arteriosus, Orthotopic Heart Transplant

<u>Low NIRS Events</u>

82% of subjects experienced one or more significant events, defined as a decrease of 20% or more in cerebral NIRS values from baseline. In total, there were 79 events. This represents an average of 1.7 events per individual undergoing surgery. The frequency distribution of these events is seen in fig. 1. These events ranged in duration from 0.5 to 40 minutes, with the average duration being 11.9 minutes.

The distribution of events (fig.2) is significantly different from a uniform distribution (chi-square 64.73, df = 6, p < 0.001, two-tailed). This was primarily driven by the disproportionate number (43%) that occurred at the beginning of cardiopulmonary bypass (p < 0.0001) (table 2). The remaining events occurred with similar frequencies before CPB was instituted, or after terminated, during the cooling or rewarming phases, upon application or removal of the aortic cross-clamp, or during the wean off CPB when the patient's heart resumed circulatory responsibilities. 6 events were not associated with any particular intraoperative stages.

Fig.1 Frequency Distribution of Low NIRS Events

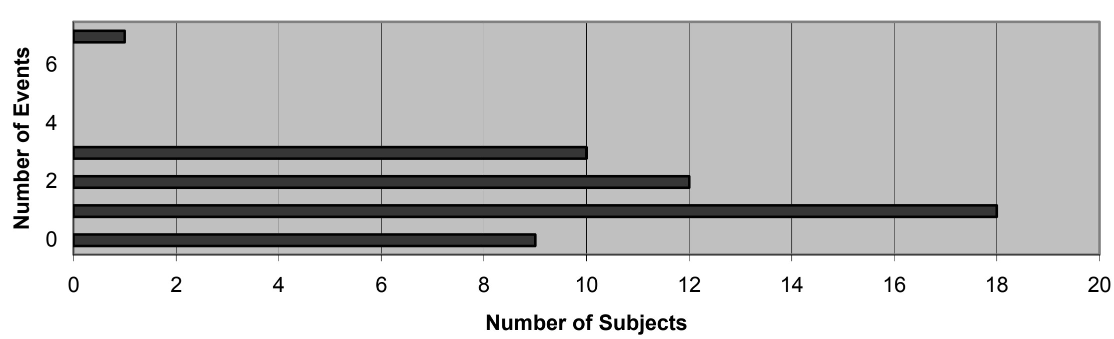

Fig. 2 Low NIRS Events by Key Intraoperative Periods

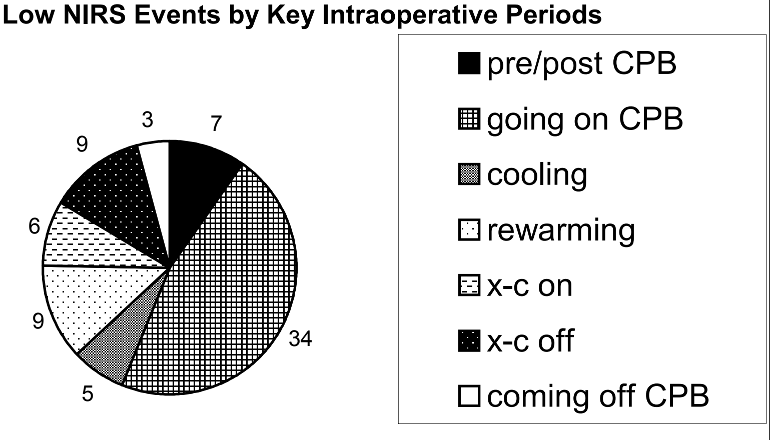

Table 2 Number of Events At Each Period

TIME PERIOD	NUMBER OF EVENTS	P-VALUE
PRE/POST CPB	7	0.25
GOING ON CPB	34	<0.0001
COOLING	5	0.07
REWARMING	9	.63
CROSS-CLAMP ON	6	0.14
CROSS-CLAMP OFF	9	0.63
COMING OFF CPB	3	0.01

Logistic Regression

In simple univariate analyses, only three variables were found to be statistically significant predictors of NIRS decreases: P_aO_2 ($p=0.0005$); hematocrit ($p<0.001$); MAP ($p<0.001$). On multiple univariate logistic modeling, the same three variables were statistically significant predictors ($p<0.05$). The final model is described in Table 3.

Table 3 Final Model

VARIABLE	CO-EFFICIENT	95% CI
P_aO_2	0.02	[0.008,0.021]
Hematocrit	0.59	[0.28, 0.90])
MAP	0.19	[0.092, 0.288]

This implies that a decrease of 10 torr in p_aO_2 was associated with an odds ratio (for NIRS decline) of 1.22; a 3% absolute decrease in hematocrit was associated with an odds ratio of 5.83; a decrease by 5 mmHg in blood pressure was associated with an odds ratio of 2.59.

Discussion

As previously stated, near infrared spectroscopy is a technique with novel applications. Several randomized studies have demonstrated some benefit to adoption of this neuromonitoring technique during adult cardiac surgery. The best pediatric evidence is provided by a retrospective review using a historical cohort for comparison.[21] However, little detail of specific NIRS changes or their correlates was included.

This study confirms that application of NIRS is feasible across a wide range of ages and sizes and provides relevant data in a cohort of pediatric patients with diverse cardiac pathologies. Throughout the study we consistently found that the probes were easily applied to patients with weights far lower than the recommended 4kg. We encountered no difficulties applying bilateral monitoring to neonates or even premature infants.

Furthermore, this study demonstrated that significant decreases in NIRS, occur in a majority of patients, with most patients experiencing two significant tissue desaturations during their operative course. On average these events last 12 minutes. This implies that most patients experience cerebral hypoxia of sufficient duration and frequency to potentially cause neuronal injury. It is plausible that recurrent intraoperative cerebral hypoxic episodes account for a component of the neurodevelopmental delay and dysfunction seen in this population postoperatively.

This study also demonstrated that significantly more events occur while going on bypass than would be expected by chance, if events occurred randomly during the monitored time period. Likely, this is due to the decreases in hemoglobin and mean arterial pressure seen at that time.

Logistic regression, in which each patient served as their own control and thus minimized potential confounders, provided information on correlated variables. Like previous studies, we demonstrate no consistent relationship between pump flow and NIRS in our study population; however, this may be a result of the minimal variability seen in pump flows intraoperatively. Once optimal flow is achieved, it is only decreased in response to surgeon demand, or an intraoperative event. However, we were able to demonstrate that clinically significant decreases in NIRS are consistently associated with hemodynamic and respiratory parameters: MAP, P_aO_2, hematocrit. The odds ratios associated with small-to-moderate variations in these parameters are not insignificant. A decrease of 10 torr in P_aO_2, which represents 3-10% of standard intraoperative values, was associated with an odds ratio (for NIRS decline) of 1.22; a 3% percent absolute decrease in hematocrit (again 10% or less of the targeted intraoperative value) was associated with an odds ratio of 5.83; a decrease by 5 mmHg in mean arterial blood pressure (10-20% of targeted values) was associated with an odds ratio of 2.59

In comparison with some previous work, our results support those studies which demonstrated correlations between arterial saturations[22,23,24], red blood cell measures[25,26,27], or MAP[28,29] and NIRS values. Studies which did not demonstrate these correlations may have had less variation in arterial saturations[30,31] or hemoglobin levels[32], or simply a lack of power, making it more difficult to confirm in their analyses. Other studies may have failed to show similar results as they considered variables in isolation. Limitations of this study include the small, heterogenous clinical population, which we felt to be at least partially balanced by the short recruitment period, and the single-center, single-surgeon approach.

Conclusion

This study accounts for the interaction and co-occurrence between multiple variables, and demonstrate that mean arterial pressure, blood oxygen content and carrying capacity (hematocrit) are significantly and independently associated with NIRS decreases. NIRS may potentially play a role in intra-operative cerebral protection by guiding hemodynamic and respiratory management; however, prospective randomized studies are still needed to conclusively demonstrate an improvement in outcome to this population.

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Manuscript Two: High Near Infra-Red Spectroscopy Measurements: An Ignored Phenomenon?

The previous manuscript firmly rooted this thesis in the pediatric population, describing the incidence, frequency, and timing of low NIRS values. Furthermore, it established a relationship between NIRS decreases and physiologic variables.

The manuscript: "High Near Infra-Red Spectroscopy Measurements: An Ignored Phenomenon?" is the second of three presented in this thesis. As part of the overarching goal of the thesis to better understand NIRS in this patient population, the objective of this paper was to attempt to provide information about NIRS values in excess of 20% greater than baseline. The definition of what constitutes a significantly high value was in parallel with that used for low values in the published literature. In addition to providing more information regarding NIRS in this patient population, it also addresses a heretofore unaddressed facet (i.e increases) of the information provided by NIRS.

High Near Infra-Red Spectroscopy Measurements: An ignored phenomenon?

Hill SJ, Lavoie J, Rohlicek C, Dougherty G, Tchervenkov C

Abstract

Background: *Near Infra-Red Spectroscopy (NIRS), as a measure of cerebral tissue oxygen content, has been proposed as an intra-operative neuromonitoring technique to improve neurological outcome following congenital cardiac surgery. To date, the focus has been on avoiding low NIRS measurements or significant decreases below the patient baseline. High NIRS measurements, on the other hand, have been essentially ignored, and may represent a potentially harmful excess in cerebral blood flow and oxygen delivery. We sought to determine the frequency of significant NIRS increases, and to assess physiological variables with which such events are correlated.* ***Methods:*** *Prospective data collection in a cohort of 50 patients undergoing operations requiring cardiopulmonary bypass for congenital heart malformations. Logistic regression was used to model the dichotomous outcome variable (i.e. a significant increase in NIRS value).* ***Results:*** *The population included 12 neonates, 17 infants, and 21 children. Sixty six percent (33/50) manifested at least one significant increase in NIRS (20% above baseline), with an average of two per patient. Mean duration of such increases was 31.1 minutes. Forty-three percent (31/71) of high NIRS values occurred at a time when the patient was not supported by the cardiopulmonary bypass machine. In simple and multiple univariate regression, only* p_aCO_2 *was found to be statistically significantly associated with high NIRS values (*$p<0.01$*). A 1 torr increase in* P_aCO_2 *was associated with a 2.40 fold increase in odds of a high NIRS value.* ***Conclusion:*** *Significant increases in NIRS occur in a majority of patients, and are associated with in* p_aCO_2*. The relationship between* P_aCO_2 *and NIRS values is likely the result of cerebro-vasodilatory effects of increased* P_aCO_2*. The clinical significance of these high NIRS values remains to be elucidated.*

INTRODUCTION

Over the last 50 years, there have been significant advances in pediatric cardiac surgery. Neonates, infants and young children routinely survive these procedures and can hope to lead full and successful lives. However, in recent years, there have been numerous reports of persistent neurological deficits in children surviving congenital cardiac surgery. These include both severe and mild neurodevelopmental delays. Post-operative deficits have been noted in language development, gross and fine motor skills, behavior, and social interaction.[1,2,3,4,5,6] The possible etiology of these adverse neurodevelopmental findings is multifactorial and may include genetic factors, fetal development and blood flow patterns, perioperative, intraoperative, and postoperative factors.[7]

Amongst other attempts to improve neurodevelopmental outcome, transcranial Near Infra-Red Spectroscopy (NIRS) has become increasingly used intra-operatively to monitor regional cortical oxygen saturation (rSO_2). Changes in rSO_2 are believed to reflect imbalances in tissue oxygenation—mismatches between oxygen supply (determined by local blood flow, blood oxygen carrying capacity and concentration) and demand.[8] The hope is that continuous monitoring of NIRS during pediatric cardiac surgery will allow prompt detection and correction of perturbations in cerebral oxygen delivery and demand. Austin et al noted that interventions based on neurophysiologic data accumulated intraoperatively by NIRS, transcranial Doppler, and electroencephalogram on pediatric patients decreased both the incidence of postoperative neurological adverse events and the length of hospital stay.[9] Iglesias et al., in a randomized controlled study, demonstrated that in adults undergoing cardiac bypass grafting, maintaining NIRS greater than 75% of baseline was associated with decreased length of stay in hospital.[10] At present there exists no published long term outcome data.

Low NIRS values have been correlated to arterial and jugular venous oxygen saturations, hematocrit, mean arterial pressure, P_aO_2 and P_aCO_2.[11,12,13] However, high NIRS values have not been adequately assessed and may also pose a risk. Hyperoxic reperfusion may exacerbate hypoxic-ischemic reperfusion (HIR) injury.[14,15] Isolated hyperoxia could impose oxidative stress causing free radical formation during cellular metabolism, which is damaging to intracellular environments[16,17]. To date, however, no study has examined these (high rSO_2) events, which represent local hyperoxia.

In this study of 50 consecutive pediatric congenital cases requiring cardiopulmonary bypass, we sought to determine the frequency and timing of significant increases in NIRS values. Furthermore, we attempted to correlate their occurrence with changes in relevant hemodynamic and physiologic variables.

MATERIAL AND METHODS

Study design

Intraoperative NIRS monitoring was implemented at the Montreal Children's Hospital – McGill University Health Centre in September 2005. We studied all children undergoing open-heart surgery requiring cardiopulmonary bypass (CPB) between September 2005 and March 2006. All were operated by a single, experienced, surgeon (CT) and underwent continuous intraoperative NIRS monitoring. Data were prospectively gathered from operating room records, perfusion records and the NIRS device.

Population

This cohort of 50 children included 12 neonates (30 days or less), 17 infants (31 to 365 days), and 21 children (older than 1 year). Ages ranged from 1 to 3869 days (10 years, 7 months) with a mean of 833 days (2 years, 3 months) and a median of 165 days (5 months). The average age in each category was 7 days, 133 days, and 5.2 years respectively. The anatomic diagnoses are listed below in Table 1. The sample included 32 males (64%) and 18 females (36%). Seventeen patients (34%) exhibited no significant increases in NIRS values throughout their monitoring and were thus excluded from the regression models.

Table 1 Subject Diagnoses

DIAGNOSIS	**# OF SUBJECTS**
Tetralogy of Fallot	9
Left Heart Obstruction (Subaortic Stenosis, Aortic Stenosis,)	8

Ventricular and/or Atrial Septal Defect	6
Atrioventricular Septal Defect	6
Pulmonary Valve/Right Ventricular Outflow Tract Obstruction	5
Transposition of the Great Arteries/ Double Outlet Right Ventricle-TGA type	4
Mitral/Tricuspid Valve Pathology	3
Double Inlet Left Ventricle	2
Total Anomalous Pulmonary Venous Connection	2
Other *	5

* Includes one of each: Aortopulmonary Window, Cor Triatriatum, Double Chambered Right Ventricle, Truncus Arteriosus, Orthotopic Heart Transplant

Monitoring Protocol

As part of our clinical protocol, all children underwent physiological and neuromonitoring. The physiologic variables recorded included pH, p_aO_2, p_aCO_2, hematocrit (hct), temperature, pump flow indexed to body surface area, and mean arterial pressure (MAP). The first four were measured with a combination of sequential or in-line blood gas analysis, the latter being used only while on cardiopulmonary bypass (CPB). Temperature was measured via a nasopharyngeal thermometric probe. Continuous pump flows were provided by the CPB machine. Blood pressure (MAP) was followed using an invasive blood pressure line.

The Somanetics INVOS 5100B Cerebral Oximeter was used to monitor NIRS values. Single-use, disposable sensors were placed over each eyebrow pre-anesthesia, while the patient was in an awake but restful state to capture bilateral baseline values. When this was not feasible the baseline was considered to be the first consistent NIRS reading displayed after the patient entered the operating room. If the patient was not hemodynamically stable, establishing the baseline was postponed until the patient was restored to a stable condition.

Data

Descriptive data were summarized using means with standard deviations, or proportions, as appropriate. Differences were tested using basic statistical tests, such as the Student's t-test or the chi-square test. Using simple and multiple logistic regression models, differences from baselines in all independent variables were compared at times of high NIRS values with those at time of recovered NIRS values.[1] Each patient thus provided their own control data. When data were not available, values of zero were imputed in order to put the emphasis on disproving the null hypothesis. All statistical analyses were done using SAS software. We required a level of significance of $p < 0.05$.

Data Analysis

Results are expressed in terms of odds ratios with 95% confidence intervals. Odds ratios describe the difference in the odds of a high NIRS value occurring with a 1 unit change compared to baseline in the dependent variable: a change in ΔP_aCO_2 or ΔP_aO_2 of 1 torr; a change in Δtemperature of 1 degree Celsius; a change in ΔMAP of 1 mmHg; a change in Δindexed pump flow of 1 $l/min*m^2$. However, because pH and hct vary in one hundredths of units (i.e. 7.40 to 7.39, and 0.32 to 0.31 respectively) these were multiplied by 100 to give the odds ratios practical meanings. Thus the OR for the change in ΔpH and Δhct variables represent the difference in odds of a high NIRS occurring when pH or changes by 0.01 unit. I.e. from 7.40 to 7.39 or from 32% to 33%.

Results

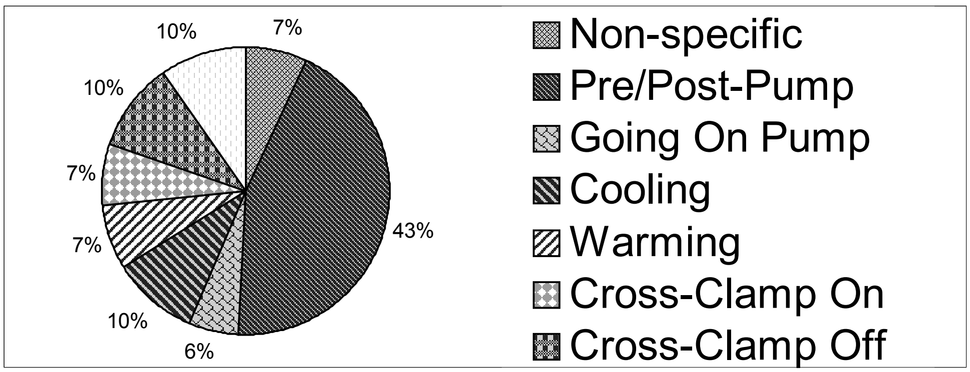
Amongst the 33 patients (66%) manifesting at least one significant increase, the number of significant increases per subject ranged from 1 to 7. The mean, modal, and median numbers of significant increases per subject were 2.2, 1, and 2, respectively.

These events lasted 1 to 220 minutes (mean 28.5). There were 73 events in total for analysis. 34% (25/73) followed a NIRS values LESS than 20% below baseline. 43% (31/73) of events occurred while the patient was not on bypass, with two thirds of these

[1] See Figure 1 in Methods

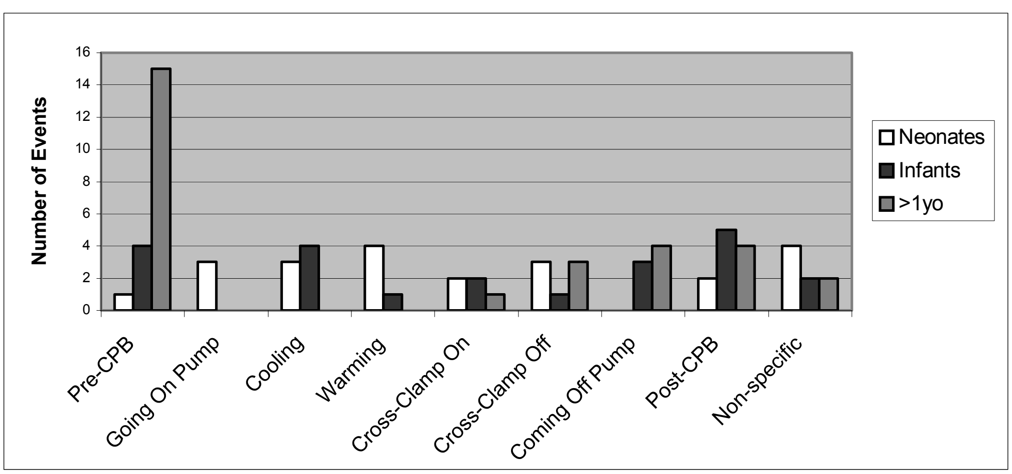
occurring before the patient went on CPB (20 vs 11). Less than 10% occurred during each of: cooling, cross clamp placement, cross clamp removal, and weaning from bypass. Figure 1 demonstrates the timing of high rSO_2 events.

Fig.1 High rSO_2 Events, by Key Intraoperative Periods



The distribution of the timing of events by gender was examined, with no statistical difference found. Neither were any statistically significant differences seen between the distributions of the timing of events by cyanotic status. In figure 2, which presents the distribution of timing of events by categorical age group, older children (>1 year old) are seen to have significantly more events prior to cardiopulmonary bypass than either of the other age groups. Only 6 of these children were cyanotic.

Fig.2 Timing of Events, by Age Category



We then examined the frequency and mean duration of events, comparing males and females, cyanotic and non-cyanotic pathologies, and age categories (Table 2). The only significant finding was that the average duration of events was shorter amongst non-cyanotic patients than their cyanotic counterparts (p = 0.003, two-sided t-test).

Table 2 Duration Frequency and Mean, by Categories

CATEGORY	MEAN BASELINE	# EVENTS/PT	EVENT DURATION
Male	65.3	1.5	30.6
Female	65.4	1.4	25.1
Cyanotic	62.4	1.6	37.7
Non-Cyanotic	67.3	1.3	15.4
Neonate	60.3	1.8	35.5
Infant	61.9	1.3	33.0
> 1 year old	71.3	1.4	29.7

<u>Logistic Regression</u>

In both simple and multiple univariate regression, only ΔP_aCO_2 was found to be a statistically significant associated with NIRS increases ($p<0.01$). The coefficient for ΔP_aCO_2 was 0.874 (95% CI 0.79-0.96). A 1 unit increase in ΔP_aCO_2 (1 torr) was thus found to be associated with a 2.4 fold increase in odds of a significant increase in NIRS reading.

Discussion

In this study, we sought to determine if we could identify hemodynamic and physiologic variables that could be correlated with significant increases in NIRS values. Variables assessed included mean arterial pressure, arterial pH, p_aO_2, p_aCO_2, patient body temperature, hematocrit and cardiopulmonary bypass flow rates. No other study has specifically examined correlates of these events. In a previous pediatric study, hematocrit and mean arterial pressure were found to be independent predictors of rSO_2 decreases.[18]

Our initial expectation was that the same variables would be important factors in rSO_2 increases. However, we found only P_aCO_2 to be a significantly associated with high NIRS values. This finding is supported by two studies in the adult population demonstrating that arterial P_aCO_2 or end-tidal CO_2 correlate with rSO_2 values[19,20].

We also examined critical time periods during surgery to see if any presented a higher risk of rSO_2 increases. The majority of events occurred before or after the patient was on bypass, at a time when the anesthetist was in control of the respiratory parameters, but did not have access to continuous arterial blood gas monitoring.

Finally, we described the events seen in different subpopulations, noting that children with non-cyanotic pathologies had significantly shorter events than cyanotic patients.

Event definition

What constitutes a significant increase in rSO_2 is difficult to ascertain in the absence of clinical neurodevelopmental outcome data. We have used the same criteria of a 20% change from baseline measurements as has been applied in the literature concerning decreases in rSO_2.[9] As with any conversion of a continuous variable into a categorical variable there exists the potential for non-differential misclassification bias, wherein true events are not labeled or captured as such, and spurious events are included as true. This causes possible loss of information. However, this bias generally weakens associations, and is unlikely to be a source of significant type 1 error[21].

The role of CO_2 and cerebral blood flow

Provision for cerebral cellular needs is safeguarded by a series of innate pathways, which maintain cerebral blood flow within a very tight range despite variation in other physiologic circumstances. This cerebrovascular pressure autoregulation (CPA) normally holds for a wide range of changes in blood pressure and blood oxygen content.[22] When homeostatic mechanisms fail, though, a fairly direct correlation is seen between cerebral perfusion and systemic arterial blood pressure in head trauma patients[23], premature infants[24], and infants undergoing cardiac surgery[25].

One well-known important factor influencing cerebral blood flow is P_aCO_2. Within normal P_aCO_2 ranges, cerebral blood flow velocity will increase by 3-4% for every mmHg increase in P_aCO_2, while a decrease in P_aCO_2 induces cerebral vascular vasoconstriction.[26] This phenomenon has been quantified in near-term sheep, wherein cortical oxygen tension increased 1 torr for every 3.2 torr increase in P_aCO_2.[27] The concept of autoregulation interference is especially important when a subject is anesthetized.[28] Inhaled anesthetics may be particularly disrupting, although this phenomenon does appear to be dose-dependent[29], and not all reports agree[30]. Bassan's group showed that 13% of infants undergoing cardiac surgery demonstrated a loss of CPA in the early post-operative period, especially when P_aCO_2 was high.[22] Thus it is not surprising that this population is at risk of CPA failure, nor that this is likely to occur intraoperatively while anesthetized, nor that P_aCO_2 is an important predictor.

Problems of excess oxygen delivery

Hyperoxia is damaging to cells in many organs, including the lung and brain[31]. At the endothelial/epithelial level (i.e., the components of the blood brain barrier) the cells are both the target and source of reactive oxygen species (ROS), at least partially via NADPH oxidase. These ROS then proceed to oxidize lipids and protein sulfhydryl groups, inactivate enzymes, damage DNA, and deplete cellular reducing agents. This leads to: 1) cell death via a combination of apoptotic and necrotic pathways; 2) activation of the cellular stress/survival response via release of free radical detoxifying enzymes; 3) induction of an inflammatory response; 4) cellular growth arrest due to DNA and enzyme oxidation.[32]

In hypoxic-ischemic reperfusion injury, the severity is related to the injury induced in both phases. Hypoxia or ischemia result in an intracellular energy failure. Reperfusion triggers a series of pathways which, among other things, result in the formation of reactive oxygen or nitrogen species when oxygen supply returns; these free radicals then cause oxidation of lipids, proteins and nucleic acids.[33] If the free radicals overwhelm the cell's antioxidant defense, this results in cell injury and possibly cell death. For years, hyperoxia following ischemia was routine under the belief that an oxygen deficit needed to be replaced. Recently, the possibility that hyperoxia further worsens the effects of hypoxia/ischemia, due to superfluous reactive oxygen species, has been evaluated. There is a growing body of literature describing how room air (versus 100% oxygen) resuscitation of neonates may be more successful because it is not associated with secondary oxygen free radical injury. Monkebey et al demonstrated that resuscitation of asphyxiated piglets with 100% oxygen was associated with higher MMP-2 activity, presumably due to augmented oxidative stress, than resuscitation with room air.[34] Klinger et al demonstrated that the risk of adverse events following the birth of a neonate with hypoxic ischemic encephalopathy due to perinatal asphyxiation was elevated with severe hyperoxia compared even to mild hyperoxia.[35] Vento et al provided further evidence for normoxic resuscitation in moderately asphyxiated neonates.[36]

Limitations

Limitations of our study include the small, clinically heterogeneous population. The small sample size may limit the study power to identify statistically significant variables. Furthermore the heterogeneity likely increases the variance. Small samples are, however, fairly standard in scientific papers on congenital cardiac surgery — a reflection of the relative rarity of the disorders. These disadvantages are balanced to some extent by the strength of a series of patients close together in time operated by a single surgeon in a single center. Further, the data were gathered prospectively intraoperatively, which reduces the possible introduction of observer bias. The physiological plausibility of the single predictor for increases in rSO_2 offers support for our observation. The last limitation of this paper is the absence of an outcome assessment demonstrating that high NIRS values are associated with neurologic morbidity. NIRS values reflect the balance between cerebral oxygen supply and demand; these periods represent significant over supply, or relative hyperoxia, which is known to be injurious. However, the goal of this paper was not to reprove that, but rather to document and qualify a previously unrecognized phenomenon which may be injurious. We expect future studies will address the clinical relevance of these events.

In conclusion, this paper identifies the potential importance of tighter control of carbon dioxide in congenital cardiac surgery, particularly before and after cardiopulmonary bypass. However, prospective, randomized studies will be required to demonstrate that this is of clinical significance.

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Manuscript Three: Bilateral Near Infra-Red Spectroscopy: Information Provided by the Second Probe

The previous two manuscripts presented our data on NIRS in the pediatric population, describing incidence, frequency, timing, and sub-populations at increased risk for NIRS value more than 20% above and below baseline. Biologically plausible significant associations were found for various physiologic variables.

The final manuscript presented in this thesis: "Bilateral Near Infra-Red Spectroscopy: Information Provided by the Second Probe" continues to describe the behaviour of NIRS in a pediatric population undergoing open heart surgery requiring CPB. It extends the range of the thesis, to address a basic issue of monitoring methodology: namely, that the best placement of the sensors remains unresolved. The objective of this paper was to attempt to provide data upon which one could inform the decision of placement. This was done by comparing the information gathered from either sensor. We built on the work presented in the first two papers by incorporating both high and low NIRS values, and presenting the information separately.

Bilateral Near Infra-Red Spectroscopy: Information Provided by the Second Probe

Hill SJ, Rohlicek C, Lavoie J, Dougherty G, Tchervenkov C

Abstract

Background: *Near Infrared Spectroscopy (NIRS) may reduce post-operative neurologic adverse events. However, use varies between centers, with a single probe placed centrally or unilaterally, or bilateral probes placed frontotemporally. Case reports have indicated asymmetries. Two larger studies have examined the data obtained from bilateral measurements. No other study has systematically analyzed the information received from the second probe.* ***Objective:*** *Determine if having a second NIRS probe adds significantly to information gathered intraoperatively.* ***Methods:*** *A prospective cohort of 65 patients (41 male, 40 cyanotic) undergoing pediatric cardiac surgery involving cardiopulmonary bypass underwent intraoperative monitoring with bilateral NIRS. Significant unilateral deviations from baseline (20% or greater) were identified. Analyses considered only those unilateral deviations (right-left discrepancies) lasting 2 minutes or longer. Demographic data were collected from the chart.* ***Results:*** Increases: *144 unilateral deviations occurred. These occurred more often amongst cyanotic patients (RR 3.8) and males (RR 1.7).* Decreases: *93 unilateral deviations occurred. These occurred more often amongst cyanotic patients (RR 2.3) and males (RR 1.5).* ***Conclusion:*** *A second probe identifies significantly more (33%) deviations from baseline, particularly in cyanotic and male patients. Further study is needed to demonstrate that these NIRS events can be routinely resolved, and that this benefits patient outcome.*

Introduction

Due to increased survival rates and decreased residual cardiac lesion incidence, neurological abnormalities has risen to the forefront of post-operative concerns amongst pediatric cardiac surgery patients. Concomitant with other measures to reduce peri-operative injury, neuromonitoring techniques have been developed. Near Infrared Spectroscopy (NIRS) is increasingly used to identify and limit periods of potential mismatch between cerebral oxygen supply and demand. Up to 73% reduction in adverse neurological events associated with pediatric cardiac surgery has been reported following adoption of a neuromonitoring technique involving NIRS[1].

Many studies have been published on the topic of cerebral NIRS in the last few years. Unfortunately, usage of the technology varies between centers. There exist two different monitors, based on different principles. These have been compared elsewhere, with reasonable correlation of results when used to measure changes from baseline[2]. Furthermore, probes have been placed bilaterally, unilaterally and centrally. Some centers are even placing a sensor on somatic sites. It is impossible to interpret the literature with certainty until usage of the technology becomes standardized, and it is impossible to standardize use without further information on each method.

Two adult cases and one pediatric case indicating asymmetries have been published, each arguing for the need for bilateral monitoring. Janelle described an adult undergoing emergent surgery for an aortic dissection with bilateral NIRS and electroencephalographic monitoring[3]. Despite originally having symmetrical values and activity, partway through the repair the right side was noted to desaturate, concomitant with an isoelectric encephalogram. This allowed the surgeon to temporarily abort aortic valve replacement and repair the arch, with improvement on neuromonitoring. Bar Yosef described a coronary artery bypass graft patient with vertebral subclavian steal who began the surgery with discrepant right and left baselines[4]. During the surgery the values neared each other at their lowest values on cardiopulmonary bypass, and post-operatively separated out again. The steal syndrome was diagnosed due to the NIRS findings. A third case report was recently published, wherein during repair of tetralogy of Fallot, in a 16-month old, after cannulation, a unilateral desaturation was noted on the right[5]. Oxygen and carbon dioxide partial pressures were confirmed to be within acceptable limits, and a mild anemia was treated, with no resolution. Increased mean arterial pressure led the authors to realize that the aortic cannula's position was suboptimal. After adjustment thereof, all parameters rapidly returned to normal. Despite all of these case reports being interesting, none demonstrated a conclusive benefit to the second sensor, as we have previously discussed[6].

In the pediatric population, two studies have examined the question of asymmetries in NIRS readings. Andropoulos et al examined the question of bilateral monitoring in a series of neonates undergoing arch reconstruction, using regional low-flow cerebral perfusion[7]. They noted a high degree of correlation between the two sides before regional low-flow perfusion was instituted. However, this correlation decreased markedly during the low-flow states and did not recover entirely thereafter. Current literature standards are to consider values more than 20% below baseline to be clinically important in the genesis of neurologic injury. In this study, Andropoulos et al considered a 10% absolute difference between hemispheres, and do not comment on whether the lower values were 20% or more below baseline values. It is unlikely that many, if any, of these discrepancies were indeed this low, as the absolute lowest NIRS value was 60%. Kussman et al evaluated bilateral NIRS at 12 time points in a more heterogeneous group of 60 pediatric patients undergoing cardiac surgery, and found no significant differences between the two hemispheres[8]. 77/634 (12%) values measured were at least 10 percent apart. Of these, in only six (8%) of all asymmetric measures was the lower value 20% or more below baseline values.

The question of the value of bilateral monitoring remains unanswered. Does the second sensor allow us to recognize significantly more events? Does having a second probe add significantly to information gathered intraoperatively? Of course, the additional information only proffers clinical benefit if these events can be resolved and if in doing so neurological injury is prevented.

Materials and Methods

In this single-surgeon, single-center cohort, we studied 65 consecutive bypass pediatric congenital cardiac cases. All cases underwent standard intraoperative neuromonitoring with bilateral NIRS probes placed frontotemporally. Baseline NIRS values for each patient were established when patients were awake, calm, and hemodynamically stable, pre-anesthesia. If this was not possible due to hemodynamic instability, baselines were established after induction and intubation.

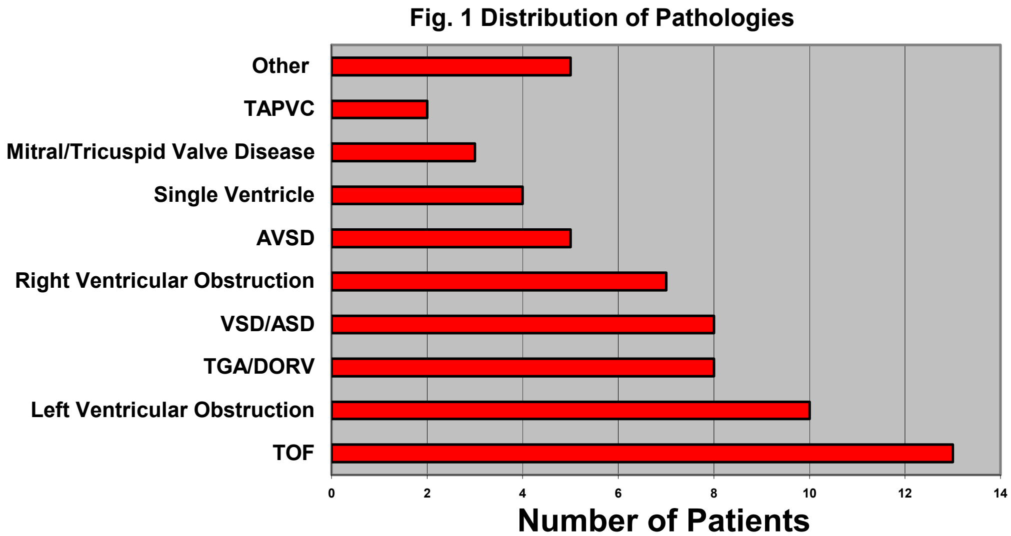
After all the data were collected, NIRS data from each case was reviewed. 20% or greater variations from baseline (increase or decrease) were deemed to be significant deviations, as is standard (at least for decreases) in the NIRS literature. Each of these events was examined to determine if it was bilateral or unilateral. It was deemed bilateral if and only if the opposite side also manifested a 20% or greater deviation in the same direction. Unilateral events of less than 2 minutes duration were not analysed, as in our opinion, shorter periods of ischemia are unlikely to be clinically relevant.[9]

Demographic data included age, weight, gender, and pathology. These were extracted from the patient chart at the time of the analysis.

The study population included 41 males and 24 females. Of these the majority were cyanotic (40 vs. 25). The ages were evenly distributed across three strata: neonates (0 – 30 days, 20 patients), infants (31 to 365 days, 22 patients) and children (greater than 1 year old, 21 patients). Median age of the population was 132 days. A wide variety of pathologies were represented. (See Fig. 1).

Statistical Analyses

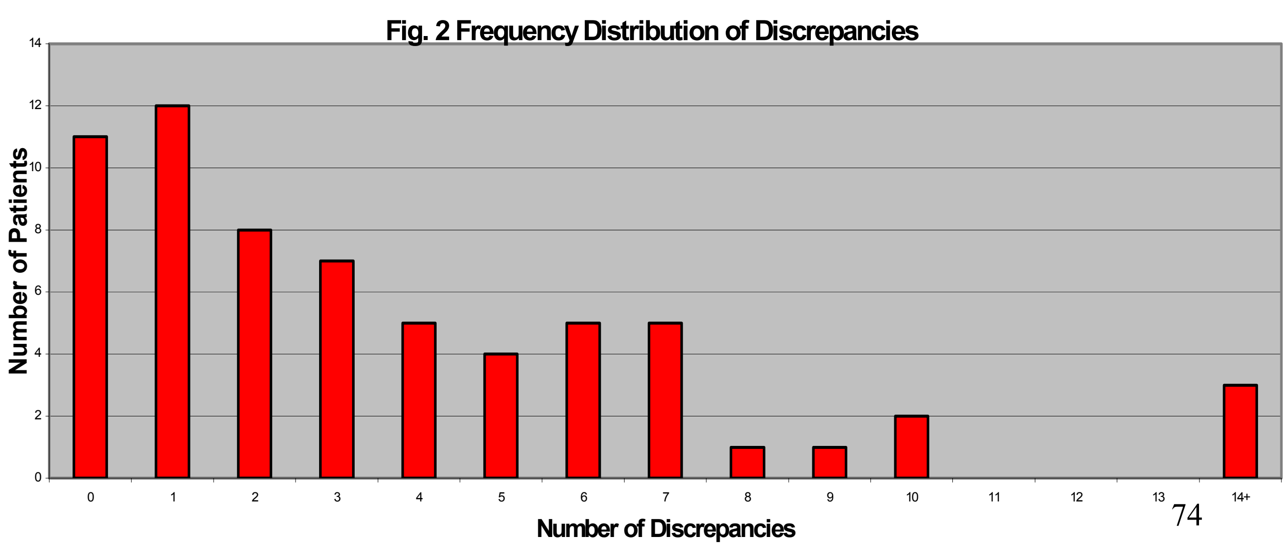
Values deviating from baseline by more than 20% were identified on each patient. When only one hemisphere demonstrated the deviation, it was considered an event. Only events longer than 2 minutes were included (as discussed above). Results were tabulated. All calculated proportions were compared using a two-tailed Student's T-test, while rate ratios were compared based on Poisson distribution. Statistical analyses were done using Excel 2000 and SISA online rate ratios comparison software[10].



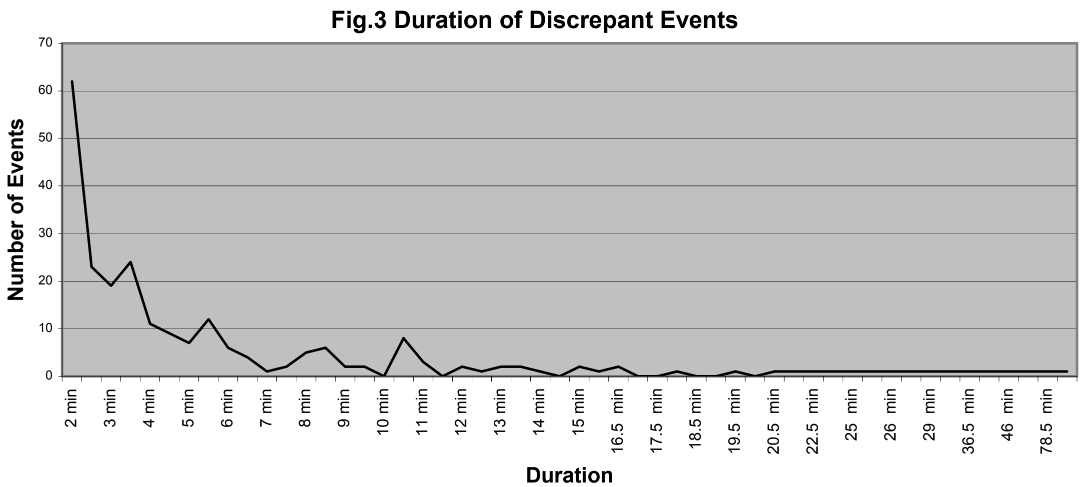
TAPVC = Total Anomalous Pulmonary Venous Connection; AVSD = Atrioventricular Septal Defect; VSD = Ventricular Septal Defect; ASD = Atrial Septal Defect; TGA = Transposition of the Great Arteries; DORV = Double Outlet Right Ventricle; TOF = Tetralogy of Fallot

Results

26% of all significant deviations from baseline were unilateral. There were a total of 237 unilateral deviations lasting 2 minutes or longer. 144 were increases; 93 were decreases. The duration of a discrepancy (a unilateral significant deviation) ranged from 2 to 80 minutes, and was on average 7 minutes long. The majority of patients (54/65) had at least one such event. The number of discrepant deviations per patient ranged from 0 to 17, with an average of 3.7 events per patient. The frequency distribution of discrepancies per patient was left skewed as is shown below (Fig.3).



The majority of events were short. 65% of all events were 5 minutes long or less (155/237 total). The duration of events is shown graphically below (Fig.3).



Increases:

144 unilateral deviations of 2 minutes or longer occurred (average of 2.2 per case). Discrepant events were more frequent amongst cyanotic patients (79%, $p<0.0001$) and males (72%, $p<0.0001$). The rate ratio of a unilateral event if cyanotic was 2.4 [95% CI (2.0,2.9)]; the rate ratio of a unilateral event if male was 1.5 (1.2,1.8).

Decreases:

93 unilateral deviations of 2 minutes or longer occurred (average 1.4 per case). Discrepancies were more frequent amongst cyanotic patients (77%, $p<0.0001$) and males (74%, $p=0.01$). The rate ratio of a unilateral event if cyanotic was 2.1 (1.7,2.7); the rate ratio of a unilateral event amongst males was 1.7 (1.3, 2.1).

Discussion

The results of this study differ from previous studies in that the majority of patients (83%) manifested significant unilateral deviations lasting 2 minutes or longer. Previous studies have shown that in only a minority of patients does the additional probe add additional information. The differing conclusions may stem from the different outcome measures. Previous studies have assessed NIRS data as a continuous variable rather than as a dichotomous outcome (presence or absence of a 20% change from baseline).

The statistically significant increased proportion of male and cyanotic patients' events is partially confounded by the disproportionate numbers of male and cyanotic patients in the study sample. The rate ratios, however, should be immune to the population proportions potential for confounding, and indicate that both increased and decreased unilateral events are more likely to occur in males and cyanotic patients. These groups may particularly benefit from bilateral monitoring.

Based on these findings, we continue to use bilateral near infrared spectroscopy monitoring in clinical practice. While this presently precludes us from using one sensor on a somatic site, newer models of the near infrared spectroscopy monitor by Somanetics have four channels, making the issue moot. However, we caution readers that conclusive evidence is still lacking to demonstrate a clinical benefit to intraoperative cerebral near infrared spectroscopy monitoring in pediatric patients, and until this is resolved, one cannot determine that two is indeed better than one.

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[10] home.clara.net/sisa

Discussion

The discussion will be divided into 5 major categories, namely: Principal Observations, Strengths, Weaknesses, Implications, Future Directions, and Summary. In these sections, we will attempt to review the major epidemiological issues relevant to this thesis.

Principal Observations:

In the drafts of the three manuscripts included in this thesis, several key observations were made. Taking each paper individually, simplifies this discussion.

Manuscript 1: One, Two, Three Strikes -- You're Out! Near Infrared Spectroscopy Event Predictors

The majority (42/50, 82%) of subjects experienced one or more significant decreases in NIRS values. An average of 1.7 events occurred per individual subject, with the majority of patients having between 1 and 3 events (one patient had 7). These events ranged in duration from 0.5 to 40 minutes, with the average duration being 11.9 minutes. Forty three percent (43%) of these events occurred at the time of instituting CPB ($p < 0.0001$). 6 events were not associated with any of the predefined, common, intraoperative stages.

In simple univariate analyses, only three variables were found to be significantly associated with NIRS decreases: P_aO_2 ($p = 0.0005$); hematocrit ($p < 0.001$); and MAP ($p < 0.001$). On multiple univariate logistic modeling, the same three variables remained statistically significantly associated with NIRS decreases ($p<0.05$). In the final model, the beta coefficients were: P_aO_2 0.02 (95% CI [0.008, 0.021]); hematocrit 0.59 (95% CI [0.28, 0.90]); MAP 0.19 (95% CI [0.092, 0.288]). This implies that a decrease of ten torr in P_aO_2 was associated with an odds ratio of 1.22; a three percent absolute decrease in hematocrit was associated with an odds ratio of 5.83; and a decrease by five mmHg in blood pressure was associated with an odds ratio of 2.59.

Manuscript 2: High Near Infra-Red Spectroscopy Measurements: What Do They Mean?

The majority of patients (33/50) manifested at least one significant increase in NIRS values, compared with their baselines. Among these, the number of significant events per subject ranged from 1 to 7. These events lasted 1 to 220 minutes (mean 28.5). There were 73 events in total for analysis. 43% (31/73) of events occurred when the patient's circulation was not being supported by the cardiopulmonary bypass (CPB) machine, with two thirds of these occurring at the beginning of the operation, before CPB was instituted (20/31). Less than 10% of events occurred during other important phases of surgery: cooling, cross clamp placement, cross clamp removal, and weaning from bypass. The average duration of events was shorter amongst non-cyanotic patients than their cyanotic counterparts ($p = 0.003$). Finally, older children (>1 year old) were seen to have significantly more events prior to CPB than the other age groups.

In both simple and multiple univariate regression, only Δp_aCO_2 was found to be statistically significantly associated with NIRS increases ($p<0.01$). The beta coefficient for Δp_aCO_2 was 0.874 (95% CI 0.79-0.96). A 1 unit increase in ΔPaCO2 (1 torr) was thus found to be associated with a 2.4 fold increase in odds of a significant increase in NIRS reading.

Manuscript 3: Bilateral Near Infra-Red Spectroscopy: Twice As Many Stickers But How Much More Information?

26% of all significant deviations from baseline (20% or greater) were unilateral. There were a total of 237 events lasting 2 min or longer. 144 were increases; 93 were decreases. The duration of an event ranged from 2 to 80 minutes, and was on average 7 minutes long. The majority of patients had at least one event (54/65). The number of events per patient ranged from 0 to 17, with an average of 3.7 events per patient. The distribution of events per patient was strongly skewed to the left.

The majority of events were relatively short. 65% were 5 minutes or less (155/237 total); this represented 69% of all events in non-cyanotic patients and 64% of all events in cyanotic patients. The duration of events is shown graphically in the manuscript.

In examining significant deviations above baseline, 144 events occurred (average of 2.2 per case). Events were more frequent amongst cyanotic patients than non-cyanotic patients (79% vs. 21% $p<0.0001$) and among males compared to females (72% vs. 28%, $p<0.0001$). The rate ratio of an event for cyanotic vs. non-cyanotic patients of a unilateral event was 2.4 (95% confidence interval [2.0,2.9]). The rate ratio for males vs females was 1.5 [1.2,1.8].

In examining significant deviations below baseline, 93 important discrepancies occurred (average 1.4/case). Discrepancies occurred more often amongst cyanotic patients (77% vs. 23%, $p<0.0001$) and males (74% vs. 26%, $p=0.01$). The rate ratio of an event if cyanotic was 2.1 [1.7, 2.7]; the rate ratio of a unilateral event if male was 1.7 [1.3, 2.1].

Strengths:

The study of upward deviations of NIRS, or high NIRS values, has heretofore not been addressed in the literature. We describe this phenomenon, qualitatively and quantitatively, and the association of these events with P_aCO_2.

The prospective study design limits to some extent the potential bias introduced by the investigators, as a result of possible data mining for associations. In a prospective design, the question is posed before data collection or analysis begins and the data collection is contemporaneous with events. Both of these points may be helpful in minimizing potential bias.

Another strength of these papers is the study population. The use of a single center, single surgeon sample may reduce significant sources of variability which could otherwise contribute noise in the observed associations. Thus the single surgeon, single center population sample likely creates a more homogenous sample, and may allow for a smaller sample size.

Another strength of this study lies in the analysis. Event data were matched to return-to-baseline data for the same patient. Furthermore, each was calculated as a change from baseline. This controlled to some degree for inter-individual variability.

Limitations:

The unblinded nature of the data collection may have allowed bias to be introduced into the data set. On the other hand, the selection bias and classification bias for events were limited to some extent by the standardized definition of events and the automated display function.

The varied ages and diagnoses of the sample, present potential limitations. The relationship between hemodynamic and other physiologic parameters and NIRS values should not depend on nor correlate with most patient demographic characteristics included. However, including such a range in the population study sample may potentially have included confounders of the investigated relationships not controlled for by measured study variables. Furthermore, one can certainly make a case for differing relationships between NIRS and physiological variables in neonates and in older children, as the mechanisms of homeostasis and cerebral autoprotection are not as yet fully developed in neonates. However, given the small number of total cases currently available at our institution, limiting the population to a given age and diagnosis was not feasible.

The sample size is something of a limitation. It would have been interesting to stratify our population, so as to examine certain sub-populations separately. For example, patients undergoing deep hypothermic circulatory arrest, with the implied absence of circulation, may be different in some important ways. As already mentioned, age would also have been a potential interesting stratification variable. Other potential effect modifiers may include gender, and specific surgical pathology. However, the sample size necessary to assess all these variables would not have been feasible at this institution, over this available time period.

The study analysis for the first two papers is based upon difference from baseline, thus all results must be interpreted within this context. One cannot extrapolate to absolute values.

Causality:

The study design, a non-randomized one, does not have the strength to firmly support claims of causality. However, interestingly several of Bradford-Hill's criteria are at least partially met, including: strength of association, consistency with previously published work, biologic plausibility, exclusion of alternate explanations and coherence.

The strength of the association is the second Bradford-Hill criterion. While all the associations described were strong enough to achieve statistical significance, the odds ratio (for a significant NIRS decrease) of 5.83, for a 3% absolute decrease in hematocrit possibly contributes to a claim of causality. The fact that the results described herein are consistent with some of the previously published work supports the fourth Bradford-Hill criterion. The fifth criterion, biologic plausibility, is met for all of the described physiologic variable associations. The associations between events with certain intervals, is certainly plausible, as there are known blood flow changes at these times. The associations with the male gender or younger age have fewer supporting physiologic explanations. The sixth criterion, is consideration (and exclusion) of alternate explanations. There are few evident explanations for the reduction in NIRS values, other than changes in physiologic variables. However when considering which physiologic variables are of specific importance, it is clear the published results vary to an important degree. This speaks to the likelihood that there are likely many contributing causes, rather than a single one. Finally, when considering the criterion of coherence, it was worth noting that all of the associated physiologic variables are compatible with our current understanding of neurophysiology. Accepting these variables as potentially causative does not require any paradigm shifts.

Implications:

If we accept the supposition that the changes in correlated variables are at least a contributing cause to the changes in NIRS, then the assessment and determination of factors associated with significant deviations from baselines, implies a potential to intervene. Knowing at least some of the factors causing excessive or insufficent cerebral oxygen delivery, empowers clinicians to attempt to intervene upon these factors and maintain NIRS values within 20% of their individual baseline values. The hope is that this will result in lower rates of post-operative neurological sequelae such as seizures, developmental delay, and attention-deficit disorder.

The lack of neurological outcome data from this study, limits its clinical relevance. The inability to associate events, or increased frequency or duration thereof with adverse sequelae leads one to ask the age-old question: so?. The description of variables associated with events is only relevant to clinicians if events have a negative/positive effect on the patient. However, this was not the purpose of this particular study. Rather, this study sets the stage for future work (see future directions).

The third paper assessed the merits of bilateral cerebral monitoring. In an era where many researchers and clinicians are interested in assessing somatic (characteristic of the body as oppose to the brain) NIRS as well, but must function within the limits of the NIRS device, the results pose an interesting dilemma. Many machines have only 2 channels. The results of our analysis demonstrated that a significant number of deviations occur unilaterally, and thus using one of these 2 channels elsewhere would deprive the clinicians of potentially valuable neuromonitoring information.

Future Directions:

There remains much work to be done in the field of perioperative neuromonitoring in pediatric congenital cardiac surgery. Not the least of which, is the replication of our results in a different patient population. The question of specifically where the second lead should be placed remains unanswered. More importantly though, the central question of correlation to long-term outcomes remains unanswered. A randomized control trial is likely needed to demonstrate that when aberrant NIRS values are acted upon, in order to terminate or lessen the severity, the population manifests improved outcomes.

Summary:

In summary, we believe that our research has provided useful information to some of the background questions related to the subject of NIRS neuromonitoring. We have described, quantitatively the events seen in this population. We have been able to elucidate significant physiologic variables associated with important deviations from baseline, in either direction. We have described to some extent which patients appear to be more “at risk” for these events. We have observed bilateral monitoring. None of these points answer the question of the preventive utility of NIRS monitoring, but they may provide a helpful framework to allow for that question to be posed and answered.

Appendix A: Weak Acid Dissociation and pH

Weak acids dissociate incompletely in water, leaving the solution a mixture of ionized and dissociated products. In the case of carbonic acid, this can be represented by:

$[CO_2] + [H_2O] \leftrightarrow [H_2CO_3] \leftrightarrow [H^+] + [HCO_3^-]$

Henderson, in 1908, described this relationship with the equilibrium equation:

$K * [CO_2] * [H_2O] = [H^+] * [HCO_3^-]$

Where K is the acid dissociation coefficient

From this rose the Henderson-Hasselbalch equation, which describes the pH, which we recall is the negative log of the concentration of H+

$pH = pK + \log([HCO_3^-]/[CO_2])$

From the first equation, we can see that increasing the CO_2 content of blood will increase both $[H^+]$ and $[HCO_3^-]$. The body conserves bicarbonate, while easily jettisoning additional hydrogen via the urine. From the HH equation, we can see that the increase in bicarbonate ions will induce more alkaline blood.

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Time	L NIRS	R NIRS	L CBFV	R CBFV	MAP	pH	pCO2	P02	Hct	temp	flow	action	resultant NIRS
BASELINE	74	75	—	—	58	—	—	—	—	—	—	—	
4:09	88	84	43	41	93	—	— (40)	— (99)	—	35.4	—	—	
4:20	91	84	31	28	53	7.37	38 (37)	441 (99)	.33	35.9	—	—	↓FiO2
4:26	79	74	25	22	55	—	— (34)	— (100)	—	36.4	—	—	
4:30	68	60	25	30	39	7.51	24	315	.	364/350	.872	ON	
4:32	71	61	34	33	48	7.48	28	402	.28	35.8/35.6	0.480	— poor drainage	
4:33	69	60	34	44	45	7.47	29	400	.28	330/36.3	0.556		
4:34	71	63	32	40	45	7.43	35	341	.28	329/36.2	0.908		
4:35	58	46	12	11	15	7.40	39	256	.27	333/35.9	0.379	X-CON	
4:37	43	31	11	11	26	7.36	45	63	.25	329/35.1	1.341		
4:40	56	49	26	21	35	7.35	50	396	.26	329/36.1	1.618		
4:43	60	54	30	20	37	7.34	46	194	.29	329/36.9	1.454		
4:46	57	60	31	19	32	7.37	44	208	.32	36.6/37.1	1.388	given rec-	
4:50	60	54	31	25	37	7.38	44	193	.33	36.7/36	1.434		
4:52	63	60	29	21	40	7.34	43	219	.33	36.8/36.8	1.40		
4:55	59	54	21	20	36	7.32	45	168	.30	36.8/37.0	1.443		
5:00	64	62	24	32	43	7.31	46	154	.31	36.9/36.5	1.420		
5:05	58	55	21	31	36	7.31	48	159	.29	36.9/36.1	1.473		
5:06	61	57	27	40	37	7.30	44	213	.28	36.4/36.2	1.437	X-C off	
5:08	71	72	34	41	44	7.33	47	270	.27	36.9/36.3	1.404		
5:15	72	70	34	43	48	7.37	43	272	.30	36.7/36.3	1.567		
5:20	81	80	45	51	51	7.35	42	258	.30	36.9/36.3	0.960		
5:25	64	69	27	32	46	7.40	35	241	.31	36.9/31.6	0.929		
5:26	58	57	22	32	36	7.38	37	114	.30	36.9/35.6	0.761		
5:29	64	64	30	41	49	7.37	35	167	.30	36.9/35.7	0.723		
5:30	76	75	37	41	56	7.37	42	268	.36	36.9/34.2	—	OFF	
5:35	81	81	41	40	65	—	— (36)	— (99)	—	36.3	—		
5:45	86	83	35	38	72	—	— (34)	(98)	—	36.3			