Project Title

Oxygen consumption-based assessments of hemodynamics in neonates following congenital heart surgery (Oxy-CAHN Study)

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Project Summary

The purpose of the Oxy-CAHN study is to improve the monitoring capabilities of newborn infants recovering from congenital heart surgery. Currently, we utilize important but unsophisticated measures, such as vital signs and lactate measurements, to monitor these patients. Although they are useful in categorizing patients as well or unwell, these signs currently lack the power quantify a patient's risk for cardiac arrest. More to the point, they are mostly indirect measures of what we really are assessing, which is tissue oxygen delivery.

Our group has significant expertise with devices which quantify the amount of oxygen that a baby consumes every minute. These values are more commonly in combination with other measures to assess nutritional and metabolism status. In critically ill patients, however, the volume of oxygen **consumed** by a patient may be limited by the amount of oxygen their circulation **delivers**. This may represent a critical relationship, which has been previously described, but not exploited for the purpose of identifying patients with critically low oxygen delivery.

The aims of this study are therefore (1) to demonstrate that oxygen consumption can be safely and precisely measured continuously in newborns undergoing one of two common congenital heart surgeries, (2) to determine whether postoperative circulatory failure is associated with a precedent change in oxygen consumption, and (3) to determine whether the addition of the oxygen-based measurements (including oxygen consumption and venous oxygen saturations) to standardly measured parameters will add power in predicting which patients will experience postoperative circulatory failure.

If successful, this study may improve our capacity to non-invasively and continuously monitor patients following the highest risk congenital heart surgeries, and in the future, to create an algorithm which quantifies a patients risk for having a cardiac arrest. This may permit providers to intervene on these patients definitively, improving the morbidity and mortality associated with congenital heart disease.

Abbreviations

Abbreviation	Meaning
ASO	Arterial switch operation
BCH	Boston Children's Hospital
BTS	Blalock-Taussig shunt
CHD	Congenital heart disease
CICU	Cardiac intensive care unit
CPR	Cardiopulmonary resuscitation
CVP	Cardiovascular Program
DSMB	Data safety and monitoring board
d-TGA/IVS	d-Transposition of the great arteries with an intact ventricular septum
ECMO	Extracorporeal membrane oxygenation
$EtCO_2$	End tidal carbon dioxide
GEE	Generalized estimating equations
HLHS	Hypoplastic left heart sydrome
HP	Hybrid palliation
PAB	Pulmonary artery band
PLOC	Postoperative loss of circulation
Qp/Qs	Ratio of pulmonary blood flow to systemic blood flow
SVC	Superior vena cava
SvO_2	Mixed venous oxyhemoglobin saturation
S1P	Stage I palliation
T3	Tracking, Trajectory and Trigger Program (Arcardia Solutions)
VCO_2	Elimination of carbon dioxide (per minute)
VO_2	Oxygen consumption (per minute)

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Background

The Importance of Oxygen Delivery

Cellular function and survival requires a continuous supply of oxygen to perform aerobic respiration. Inspired oxygen gas traverses pulmonary capillaries and binds to hemoglobin, which carries large amounts of the molecule to the systemic tissues. Systemic oxygen delivery (DO_2) is amount of oxygen carried by a given volume of blood multiplied by its flow rate (cardiac output). This represents the amount of oxygen available for tissues to consume. In healthy individuals, this supply exceeds demand by a substantial margin - some 60-70% of oxygen delivered to the tissues returns to the systemic veins unused. The volume of oxygen actually consumed by the tissues (VO_2) of course can never exceed DO_2, and is generally governed by a patient's metabolic rate. In critically ill patients, factors which are known to increase VO_2 include fevers, seizures, activity and inotrope administration to name a few. In patients who are very critically ill, DO_2 may actually decrease below a critical threshold known as 'critical DO_2' (**Figure 1**).[1] Below critical DO_2, the body's normal compensatory mechanisms (e.g. to increase cardiac output or increase the oxygen extraction ratio) are overcome, and an insufficient volume of oxygen is delivered to tissues, which in turn decreases VO_2 (since tissues cannot consume oxygen if it is not delivered).

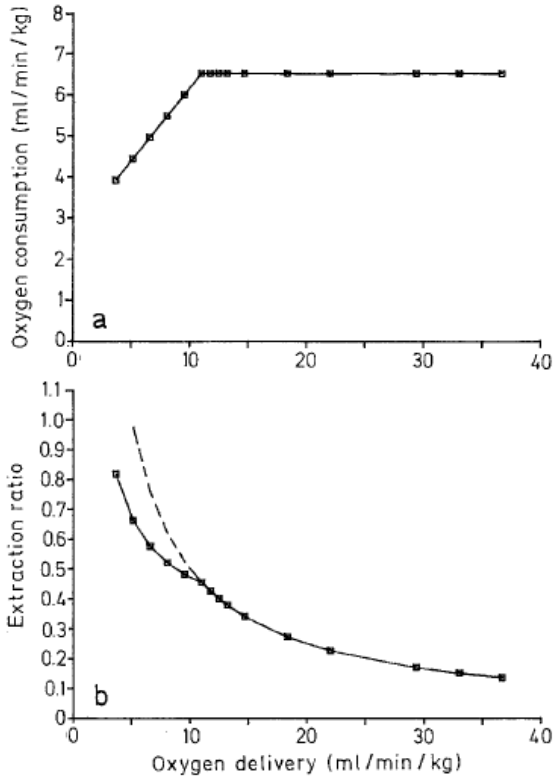

Figure 1. Oxygen delivery is the amount of oxygen carried to the tissues, and typically far exceeds that which is needed/consumed by the tissues. As oxygen delivery decreases progressively (moving right to left across the X axis), a critical threshold is reached below which oxygen consumption decreases as tissues become dysoxic (A). As tissues become progressively hypoxic, an increasing amount of oxygen is extracted from hemoglobin, increasing the oxygen extraction ratio. Figure from Schumacker, *Int Care Med*, 1987.

In critically ill patients, e.g. in newborns following open heart surgery, it is common for DO_2 to be marginal. This is evidenced by increases in serum markers of anaerobic metabolism (namely serum lactate measurements), by evidence of a high oxygen extraction ratio (low superior vena cava oxyhemoglobin saturations relative to arterial saturations), and by evidence that the cardiovascular system is compensating for inadequate cardiac output (e.g. physical signs of increased systemic vascular resistance and a fast heart rate). When the myocardium receives and insufficient amount of oxygen, tissue hypoxia ensues and causes myocardial dysfunction. Intensive care efforts often focus upon improving tissue perfusion by increasing cardiac output, and this requisitely increases myocardial oxygen demands.[2] In the most

critically ill patients, the myocardium reaches a profound state of tissue hypoxia which may cause a postoperative loss of circulation (PLOC).

HLHS and the risk of PLOC

Patients with hypoplastic left heart syndrome (HLHS) necessarily have so-called 'single ventricle physiology'. In these patients, the right ventricle pumps blood to both the systemic circulation (to deliver oxygen) and to the lungs (to pick up oxygen, **Figure 2**). Normally, these two functions occur in series, i.e. the right ventricle pumps blood to the lungs and the left ventricleto the body. In two ventricle physiology, each ventricle pumps one cardiac output. In single ventricle physiology, however, the right ventricle pumps to both circulations in parallel, requiring at least 1.6-1.8 cardiac outputs (at times 2-3 cardiac outputs),[3] which among other things causes a disproportionate increase in myocardial VO_2. In the postoperative period, the oxygen extraction capacity of myocardium may be compromised by tissue edema, systemic inflammation, and mitochondrial dysfunction following the effects of cardiopulmonary bypass. Myocardial oxygen delivery can be compromised by anemia (as a consequence of postoperative bleeding), and by inadequate coronary blood flow (especially pronounced in settings of tachycardia - which decreases coronary filling time - and of diastolic hypotension due to the presence of a systemic to pulmonary shunt).

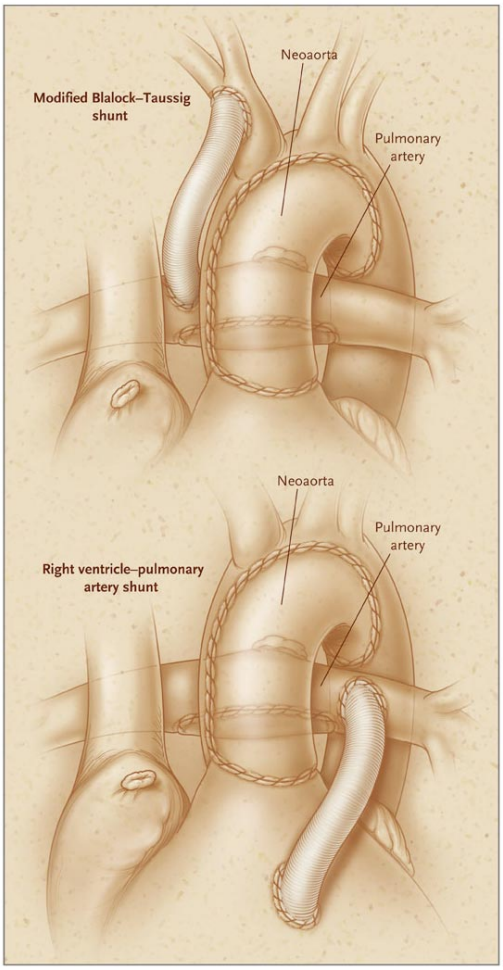

Figure 2. In patients born with an inadequate left ventricle, the right ventricle is used to pump blood to both the body and the lungs simultaneously and in parallel by connecting the pulmonary artery to the small aorta, and creating a shunt from this circulation to the lungs. This circulation leads to increased oxygen demand for the heart. When this demand is not met, myocardial dysfunction and PLOC result. Figure from Ohye, *NEJM*, 2010.{Ohye:2010kn}

In the BCH CICU, approximately 10-15% of neonates undergoing a stage I palliation (S1P) experience PLOC and receive some resuscitation, often times in the form of extracorporeal membrane oxygen (EMCO) device support. These patients often experience increased ICU and hospital lengths of stay, higher hospital morbidity and mortality, and worse neurologic outcomes.[4-6] The purpose of this study is to determine whether continuous monitoring of VO_2 and SVC saturations will allow development of signs to predict which patients are at highest likelihood of experiencing a PLOC before the event, permitting time for interventions to take place prior to an injurious or potentially lethal event.

Currently Used Markers of Oxygen Delivery

Assessing the physiologic state of patients is a complex but vitally important task. At the bedside, the clinician combines many pieces of data to assess the adequacy of end organ oxygen delivery, each of which has strengths and weakness as a clinical sign. Basic hemodynamic parameters (aka vital signs) include a patient's heart rate, arterial and venous blood pressures, oxygen saturations and temperature are central to the assessment of a patient's physiologic state, and are often the most important clues to inadequate oxygen delivery. Further to this includes markers of end organ function, such as urine output, coagulation parameter, as well as laboratory indices of hepatic and renal function add some degree of confidence that our general assessments are correct.

In patients at higher risk of insufficient DO_2, advanced monitoring techniques are commonly used. The three most commonly used techniques in routine use in neonates undergoing congenital heart surgery include (1) cerebral near infrared spectroscopy (cNIRS), (2) SVC saturation sampling, and (3) serum lactate measurements.

Cerebral NIRS

cNIRS is a technology which intends to non-invasively quantify (at least as a trend) the quantity of oxyhemoglobin versus deoxyhemoglobin within the tissue beds underlying the probe. The probe emits red light to the surface of the forehead, penetrating to the cerebral cortex of the brain. Because oxyhemoglobin absorbs green and blue wavelengths, but deoxyhemoglobin does not (hence desaturated patients appear cyanotic), the optical properties of the light returning to the sensor depend upon the oxyhemoglobin/deoxyhemoglobin ratio within the tissues that the light path crosses. The monitor we use most often (Somanetics INVOS Cerebral/Somatic Oximeter) senses light at two wavelengths (730 and 810 nm) and converts this number to a regional oxyhemoglobin saturation index. The measurement of NIRS has been correlated with jugular venous saturation in humans.[7,8] The technology was approved for pediatric use in 2005, and has been utilized in several studies of pediatric cardiac patients since that time.[9,10]

However, there are important limitations in using NIRS to assess mixed venous saturation, including the obscuring and competing signal from myoglobin in skeletal muscle, interfering with the superimposed spectral signal from red cell hemoglobin.[11] There has been a resultant lack of subsequent evidence validating NIRS with low cardiac output in children after cardiac surgery with possible risk of potential harm from uncertainty in interpretation of the recorded NIRS values.[12] Because of these limitations, the 'gold standard' for assessing cerebral oxygen delivery is therefore quantification of SVC oxyhemoglobin saturations.

SVC oxyhemoglobin saturations

Inadequate DO_2 leads to tissue hypoxia, which in turn leads to an increased oxygen extraction ratio and central venous desaturation. Therefore, quantification of oxyhemoglobin saturation from a pulmonary artery (distal to complete mixing) is considered a benchmark measurement when assessing oxygen delivery. However,

because this requires placement of a pulmonary artery catheter (which is not commonly done in children), blood is more commonly sampled from the SVC for the same purpose. In fact, SVC saturations are at times the most accurate place to sample venous blood, as many patients with congenital heart disease (CHD) have left to right shunts or even single ventricle physiology, making pulmonary artery saturations difficult to interpret.

Typically, SVC saturations are measured by intermittent sampling of blood from a catheter placed into the SVC via the internal jugular vein, or retrograde through the right atrium. The SVC saturation is used to calculate the oxygen extraction ratio, and generally values below 40-50% represent a compromised DO_2. The limitations to this technique include the following. (1) Blood must be removed from the body (including 'waste' blood which fills the catheter) which can lead to anemia. (2) Even frequent sampling of SVC blood is intermittent, and assessing responses of DO_2 to interventions can be difficult in real time. (3) Frequent entry into the central line can increase the risk of catheter related bloodstream infection. (4) In patients with profoundly low SVC saturations, small amounts of air which enter the blood gas syringe can lead to artificially higher oximetric readings.

To address these limitations, we will test a recently developed central venous catheter which utilizes in vivo reflection spectrophotometry on 4 wavelengths (PediaSat catheter; Edwards Lifesciences) to accurately quantify oxyhemoglobin saturations in blood passing the catheter tip. This catheter is placed in standard fashion, and is coated with both Heparin and antimicrobials in order to diminish the risks of thrombus formation and infection, respectively. Its insertion is similar to standard catheters which are routinely placed in the patient populations being studied here. We have chosen to utilize this catheter in this study because it addresses the pitfalls of our current standard of care above, and because it will allow a continuous, real-time assessment of cardiac output and an estimation of the ratio of pulmonary to systemic blood flow (Qp/Qs). Of note, the catheter was recently used to safely and accurately quantify SvO_2 in neonates following cardiac surgery.[10]

Serum lactate measurement

Serum lactate represents the biproduct of anaerobic respiration within the tissues, and is therefore an obvious choice as a marker of inadequate DO_2. It is commonly measured in the clinical management of neonates following congenital heart surgery. Unfortunately, serum lactate can be falsely low in extreme tissue malperfusion (it is thought that lactate does not equilibrate with the plasma in situations of extremely low DO_2), and can be falsely elevated by the use of inotropes (prototypically, epinephrine) and in hepatic dysfunction. Together, these factors make isolated measurements of lactate difficult to interpret.

It has been previously shown that in adults experiencing a cardiac arrest, a high serum lactate (>10 mg/dL) is more common in patients experiencing a recurrent cardiac arrest.[13] It is also known that serum lactate measurements may correlate with chances of survival following cardiopulmonary bypass in neonates.[14] On a population level, it is

known that patients who experience a die following a postoperative cardiac arrest have higher pre-arrest lactate levels than those who survive.[15] However, to date, this information has been of limited prospective utility in the prospective management of patients, specifically in guiding therapies to optimize DO_2.[16,17]

Oxygen consumption

As discussed above, when DO_2 decreases below the critical DO_2 threshold, VO_2 becomes pathologically supply dependent. In clinical practice, VO_2 is most commonly estimated based on normal values, though this has been shown to be an inaccurate practice.[18] Alternatively, VO_2 can be measured in intubated patients by calculating the fraction of oxygen that is inspired versus that which is expired during each breath. That information, combined with the volume of each breath, represents the volume of oxygen consumed by the patient.

Several commercially available devices have been shown to exhibit both precision and accuracy in quantifying VO_2 in newborns, even those following congenital heart surgery. For example, Li has described the VO_2 of newborns following S1P to be ~80-100 mL/min/m^2 [19], using a VO_2 monitor which utilizes mass spectroscopic evaluation of inhaled versus exhaled gases. However, none of these studies have attempted to correlate VO_2 with outcomes, neither short- nor long-term, including PLOC.[19-23]

Members of this research team have become familiar with another device used to quantify VO_2, and have utilized it in several clinical studies to date.[24,25] Over the past three years, for example, members of our group completed a study in which VO_2 and VCO_2 were quantified in postoperative Fontan patients using this device in the CICU.[24] The nursing and respiratory care staff are therefore already familiar with the machine and its use.

The device utilizes an in-line adapter which affixes to the end of the endotracheal tube, and samples gas concentrations on a breath-to-breath basis (GE Healthcare, E-CAIOVX module, Waukesha, WI). The process for gas exchange measurement has been described previously.[26] In brief, inspiratory and expiratory gas concentrations are obtained every breath utilizing a fast differential paramagnetic O_2 analyzer and infrared CO_2 analyzer by side-stream sampling. A fixed orifice, pressure differential pneumotachometer (D-lite (+) or Pedi-lite (+), GE Healthcare, Madison, WI) is used to measure gas volumes and flows and to calculate VO_2. This device has been well validated against mass spectrometry and has been found to be both accurate and precise at even low VO_2 levels.[26]

Preliminary Studies

The impetus for this study has stemmed from pre-clinical work performed by the PI. In other work, the PI studied an intravenous treatment for complete asphyxia in which oxygen gas is packaged into microparticles to be rendered injectable.[27] In this model, oxygen consumption was quantified using the GE device. We have noticed that animals with extreme, untreated asphyxia exhibited a lower VO_2 when compared to their healthy baseline, and that prior to a subsequent cardiac arrest, many animals

exhibited a pronounced decrease in their measured VO_2, a pattern which was not present in treated animals which did not experience subsequent hemodynamic instability (**Figure 3**). Having seen this pattern consistently in approximately n=40 animal experiments (weight range 2.5-4 kg), we hypothesize that in critically ill patients, VO_2 may decrease below the critical DO_2 and exhibit measureable, even striking, decreases prior to hemodynamic decompensation takes place. If this hypothesis is true, quantification of VO_2 may represent a new 'vital sign' which represents end organ oxygen delivery in critically ill patients. Identification of patients with pathologically supply dependent VO_2 may permit definitive interventions to take place, e.g. initiation of extracorporeal life support, prior to a life-threatening PLOC.

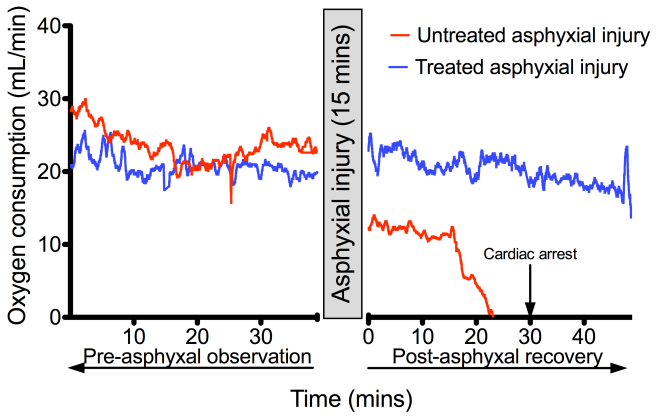

Figure 3. In a proof of concept study, VO_2 monitoring of rabbits (weight ~3 kg) undergoing a 30 minute period of observation, followed by a 15 minute period of asphyxia, then a post-asphyxial recovery. Exemplary VO_2 tracings shown of animals treated (blue line) and untreated (red line) with an intravenous formulation of oxygen which prevented severe hypoxemic-ischemic injury. Animals which suffered severe injury exhibited a significant decrement in VO_2 early during the recovery period, a pattern which worsened prior to post-asphyxial loss of circulation. Animals who experienced treated asphyxial injury had an unchanged VO_2 curve. **A central hypothesis of this study is therefore whether VO_2 may represent a sensitive, real-time, prospective, and non-invasive marker of circulatory failure and inadequate DO_2 in newborns at risk for this life-threatening problem.**

Study Objectives

Specific Aim 1. To demonstrate that oxygen consumption (VO_2) and superior vena cava (SVC) saturations can be safely and precisely measured continuously in newborns undergoing surgery for hypoplastic left heart syndrome (HLHS) or d-transposition of the great arteries with an intact ventricular septum (d-TGA/IVS).
Hypothesis: Measurement of these oxygen-based parameters will not be associated with an increased incidence of equipment-related adverse events (e.g. line displacements, inadvertent extubations) and will lead to precise and reproducible measurements of these important parameters.

Specific Aim 2. To determine whether postoperative loss of circulation (PLOC, defined as cardiac arrest requiring CPR, ECMO cannulation, or causing death) in these patients are associated with a change in oxygen consumption or SVC saturation prior to the event.
Hypothesis: PLOC will be associated with significant decreases in both oxygen consumption and SVC saturations for at least 10 minutes prior to the onset of cardiac arrest.

Specific Aim 3. To determine whether the addition of the oxygen-based measurements to standardly measured parameters (i.e. vital signs, near-infrared spectroscopy

measurements, intermittent measurements of lactate and superior vena cava saturations) add power in predicting which patients will experience PLOC. *Hypothesis: Continuous measurements of VO_2 and SVC saturations will add significantly to our ability to predict which patients will undergo PLOC.*

Study Design

We will prospectively and continuously measure VO_2 and SVC saturations in newborns undergoing stage I palliation (S1P) or hybrid palliation (HP) for HLHS (n=20) or arterial switch operation (ASO) for d-TGA/IVS (n=20), beginning at the time of first preoperative intubation and ending at the time of the first postoperative extubation. Newborns will be followed for the occurrence of PLOC as the primary endpoint. A study schematic is attached as **Appendix 1**.

Study Population

Inclusion criteria.

1. Patient from birth to 6 months of age
2. HLHS AND no prior operations AND planned S1P or HP
   OR
   d-TGA/IVS AND planned ASO
3. Written parental informed consent

Exclusion criteria.

1. Weight < 2 kg
2. Disease specific
   - **A.** HLHS patients: Infants whose surgical plan includes a neonatal biventricular repair will be excluded.
   - **B.** d-TGA/IVS patients: Newborns with any additional cardiac defect other than an atrial septal defect will be excluded.
3. Patients on ECMO preoperatively
4. Clinically significant tracheo-esophageal fistula or known preoperative air leak

Recruitment Methods. The flow of patients and the infrastructure within the CVP at BCH is ideally suited for this study. A list of planned newborn admissions, including presumptive anatomical diagnoses) is kept by the Advanced Fetal Care Program (AFCP) within the CVP, and is emailed to providers within the Cardiac Intensive Care Unit (CICU), which will be screened weekly by the study team. Additionally, the CICU census will be screened each morning by a member of the study team for patients meeting inclusion criteria. As a backup, CICU staff will be formally educated about the study and asked to page the PI upon admission of patients meeting inclusion criteria.

The early newborn period is one which is full of anxiety, stress and an overwhelming amount of information. In the spirit of achieving a more informed consent, we will attempt to raise awareness of the study in the following manner. A one-page brochure describing the study will be placed in the employee areas of the AFCP. Staff members who follow expectant mothers whose children have either HLHS or d-TGA/IVS will be

asked to give the flyer to their patients in order to allow time for parents to consider participation prior to the birth of their child. Study staff will be made available for questions by email, phone or in-person for these parents at any time. The flyer is attached as **Appendix 2**.

When patients are identified who meeting study criteria, study participation will be discussed with the treating team, specifically including the patient's cardiac intensivist and cardiac surgeon. Following the verbal assent of the team, parents will be approached for written consent.

Study Treatments

The treatment which newborns with congenital heart disease receive is complex, and is directed by a multidisciplinary team which includes a cardiac surgeon, a team of cardiac intensivist, a primary cardiologist and an array of cardiac subspecialists (e.g. cardiac catheterization staff). Patients in this protocol will be treated according to the current standard of care in the CVP by their treating teams. As this is a prospective observational study, there will be no treatments associated with the study except for the application and insertion of the relevant equipment, which is described below.

VO_2 monitoring. Currently, all patients undergoing mechanical ventilation for any reason are monitored using a capnograph, a device which features an adapter fitted onto the end of the endotracheal tube for the continuous monitoring of end-tidal carbon dioxide ($EtCO_2$), and other basic spirometric measures (e.g. tidal volume, VCO_2, lung compliance). There are several different capnograph devices in current use within BCH. However, none of these devices measure VO_2, which is a critical endpoint in our study. Therefore, patients included in the study will be monitored using a device with this capability (Datex Ohmeda Critical Care Monitor, GE Healthcare, E-CAIOVX module, shown in **Figure 4**). As discussed above, the study team has accumulated significant experience with this FDA-approved device in children, and it has been used in other clinical studies in children at BCH. All cardiac intensive care, cardiac anesthesia and cardiac ICU nursing staff will be inserviced on the equipment by a member of the study team prior to initiation of the study.

Figure 4. The E-CAIOVX module of the GE monitor to be used in this study. The plastic piece to the left fits onto the end of the tracheal tube and measures features of inhaled and exhaled breath by side-stream analysis.

In the opinion of the study team, VO_2 has not been validated as a clinically useful piece of data in this age group. Therefore, only the standard parameters of ventilation (i.e. end tidal CO_2, capnograph waveform, tidal volume and lung compliance measurements) will be displayed on the monitor for clinician use for the duration of the study; VO_2 will be recorded but not displayed on the monitor.

SVC saturation monitoring. Currently, all patients undergoing an S1P, HP or ASO routinely undergo placement of a temporary central venous catheter placed within the internal jugular vein, and terminating within the SVC. These catheters are standardly used for infusion of inotropic medications, constant monitoring of central venous pressures and the intermittent withdrawal of blood for SVC saturation measurements. These catheters are standardly 4 French in size, are 5 cm in length and contain two lumens (Cook Medical). Following admission to the CICU, these catheters are routinely treated with a Heparin infusion at 10 Units/kg/hour through one of the lumens until the time of removal.

In lieu of the standard Cook Medical catheter, the treating team will place a similar FDA-approved catheter, but which is fitted with a fiberoptic sensor which continuously records the oxyhemoglobin saturation of the blood to which it is exposed. The catheter is 4.5 French, 5 cm in length, has two lumens, and is Heparin bonded (PediaSat catheter, Edwards LifeSciences, Model# XT245HK, see **Figure 5**). The catheter comes will a sterile percutaneous insertion kit. As above, all cardiac intensivists, cardiac anesthesiologists and CICU nursing staff will receive a formal training on the insertion and care of this catheter by the company representative (Mr. Brad Cangiamila). Prior to insertion, the catheter will be calibrated using an in vitro solution which comes with the catheter. For those familiar with the device, this process will add 2-3 minutes to the insertion time. Following insertion of the catheter, the device will be attached to the study monitor (Datex Ohmeda Critical Care Monitor, GE Healthcare) via a specialized cable. The catheters will be paid for by the PI.

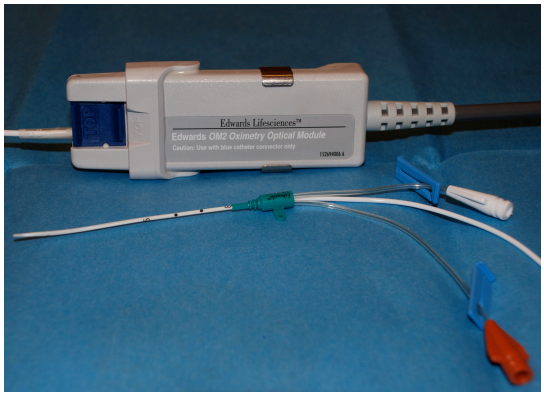

Figure 5. The PediaSat catheter to be used in this study is functionally the same as catheters routinely used in the perioperative care of newborns with CHD except that it is fitted with a fiberoptic probe at its tip which continuously reads SVC saturation.

In the opinion of the study team, the SVC saturation is a clinically useful piece of data which is routinely used at BCH in the management of patients. Because the device readings have been shown to correlate well with oximetric readings from venous blood, the SVC saturation will be continuously displayed on the study monitor for clinicans to use at their discretion for the duration of the study.

The study will end following the first postoperative extubation or removal of the central venous catheter, whichever occurs last.

Endpoints/Outcomes

Primary Outcome. The primary outcome being measured will be a composite endpoint of PLOC, including the need for CPR, the need for ECMO in the setting of CPR, or death.

Secondary Outcomes. Because Aim 3 of this study is to determine whether the aforementioned oxygen-based measurements add to the predictive power of the data standardly used to assess patients, there will be a substantial amount of data gathered, which is outlined below.

- Oxygen-based parameters unique to this study
  - Oxygen consumption (Q1 second). The VO_2 will be recorded Q1 second as part of the ventilatory parameters described below.
  - SVC saturations (Q1 second). SVC saturations as determined by oximetry will be recorded Q1 second.
- Standard of care monitoring
  - Vital signs. These data will include heart rate, arterial blood pressures, respiratory rate, pulse oximetry, atrial pressures, and central venous pressure. As discussed in detail below, these data will be extracted from an existing program which records the primary data Q5 second in time stamped fashion (T3 Program, Arcardia Solutions).
  - *NIRS*. The near-infrared spectroscopy value represents the oxyhemoglobin saturation of the deep tissues. This will be recorded Q1 second in time-stamped fashion.
  - *Ventilatory parameters*. All ventilation parameters will be recorded from the spirometry recordings from the capnograph. These data include end-tidal CO_2, fraction of inspired CO_2, respiratory rate, fraction of inspired O_2, fraction of expired O_2, peak end expiratory pressure, peak inspiratory pressure, plateau pressure, mean airway pressure, airway resistance, inpiratory-expiratory time ratio, inspiratory and expiratory times, inspiratory and expiratory tidal volume, compliance of the respiratory system, minute ventilation, VCO_2, energy expenditure, and respiratory quotient. These data will be recorded Q1 second in time-stamped fashion.
- *Standard labs* will be drawn at the treating team's discretion and gathered from the medical record each day.
  - Arterial blood gase and time drawn
  - Serum lactate and time drawn
  - SVC (or other venous) saturations and time drawn
  - Chemistry profile, complete blood count (white blood cell count, hemoglobin, hematocrit and platelet count), coagulation profile and times drawn
- Treatments
  - *Inotrope infusions* are routinely administered, often in high doses, to these patients in the perioperative setting. It is thought that these infusions affect both oxygen delivery to all tissues, as well as increasing myocardial oxygen consumption.
  - Additionally, we will record *intermittently administered medications*, such as epinephrine, calcium gluconate, sodium bicarbonate, hydrocortisone, and

thyroid replacement therapy, all of which may affect oxygen consumption and oxygen delivery as well.
    - Chest explorations and operative interventions performed at the bedside (e.g. clipping of BTS or Sano shunt) will be recorded each day from a review of the medical record, discussion with the primary team (including the bedside nurse) and the notes within the medical record.
    - Blood loss from chest tubes (in mL/kg each hour) and blood product administrations (including the blood products given and the times at which they are given) will be recorded from the medical record each day.
    - Sedatives and paralytics are routinely used and also affect oxygen consumption.
    - Diuretic medications are also routinely used, can affect preload.
    - Arrhythmias and
- Other clinical parameters
    - Urine output is a crude marker of intravascular volume and end organ oxygen delivery.
    - The presence of enteral feedings, the rate of feedings and the caloric densities will also be recorded, as these may affect a patient's systemic vascular resistance.
- Operative characteristics
    - Full preoperative and postoperative anatomic diagnoses
    - Residual anatomic defects
    - Total pump time, cross-clamp time, circulatory arrest time, regional perfusion time, minutes of continuous and modified ultrafiltration, blood products administered on bypass

Data Collection Methods, Assessments and Schedule

Outcome measurements

The majority of the endpoints presented above are routinely collected within the medical record as a part of patient care. Therefore, the majority of the data will be abstracted directly from the medical record and into a spreadsheet for data analysis by a member of the study team during each day for the duration of the study. The PI employs two full-time technicians within his lab who will assist with this labor intensive process.

- The oxygen-based measurements which are central to this study, including VO_2, SVC saturation, as well as all ventilatory parameters listed above will be saved to a computer program (S5 Collect, GE Healthcare) attached to the patient's monitor. This program saves data in time stamped fashion Q1 second.
- Time-stamped vital sign data listed above will be exported daily from the hospital's in situ T3 program (Arcadia Solutions).
- The labs, treatments and other clinical parameters (see previous section) will be extracted in time-stamped fashion from the medical record each day by a member of the study team.

Patient variables

Upon study enrollment, we will record relevant variables for the purposes of comparisons between patients, including gestational age, date and time of birth, gender, weight and length, date of admission, known medical problems, current medication list. Markers of severity of illness will include the number of organ failures, number and dosing of inotropic medications, and any positive cultures.

Adverse events
Although this is a prospective, observational study which do not anticipate will alter our standard practices, we will monitor vigilantly for complications associated with the standard therapies used in these patients for differences in study patients. Namely, we will monitor for endotracheal tube complications (e.g. ventilator associated pneumonia, accidental extubation) and for central venous line complications (e.g. catheter associated bloodstream infections).

Safety end points
Because this is a prospective observational study and is not expected to directly impact patient care, we will not have stopping rules for an individual patient per se, except if informed consent is withdrawn by a parent or team member.

Parameters for discontinuation of the research
All components of this study have been tested and validated in the critically ill newborn population. As such, we do not anticipate any technical problems with the observations proposed in this study. However, the research will be discontinued if an interim analysis shows a significant increase in the adverse events presented above compared with a retrospective control.

Adverse Event Criteria and Reporting Procedures

A data safety and monitoring board (DSMB) will be composed of two clinicians knowledgeable in the postoperative care of children with congenital heart disease. The DSMB for this study will include John Arnold, MD, Director of Respiratory Care, and staff Anesthesiologist and Intensivist at Boston Children's Hospital, and Kirsten Odegard, MD, a staff Cardiac Anesthesiologist at Boston Children's Hospital. Meetings will be held at the discretion of the DSMB members and study investigators, at least once following enrollment of the first 5 patients. The following complications will be specifically monitored for and reported to the DSMB immediately upon occurrence: accidental extubation or central venous catheter removal thought to be related to the monitoring devices (these are both extremely unlikely given that they are FDA-approved, widely used devices in children).

Data Management and Statistical Analysis

Data management methods
Upon entry into the study, each patient will be assigned a unique patient identifier which is unique from their medical record number for the purpose of patient tracking. A spreadsheet which links each patient's UPI and BCH medical record number will be

kept in a separate binder, locked in the PI's office. The UPI will be used to identify patients on all study-related materials, including the laptop used to collect data from the GE monitor (which includes all ventilation parameters and SVC measurements), and on the data collection forms. Data from the T3 system will be extracted from SQL T3 database, and stored in a deidentified manner using the same UPI.

Logistic considerations

At the time of study enrollment, baseline characteristics will be collected and recorded on a deidentified form. At the time of first intubation or CVL placement, the pole-mounted GE monitor will be brought to the room by study personnel, and data recording will begin in realtime to the S5 Collect program using an attached laptop (**Figure 6**). The program file will be saved as the patients UPI and will not contain confidential information. Care will be taken to synchronize the time stamps within each of the devices in order to ensure proper alignment of the various data sources.

Figure 6. The oxygen-based monitoring and data collection systems utilized for this study are attached to a rolling pole which can be placed anywhere around the patient and easily moved for convenience and safety.

Each day, a member of the study team will visit the patient's bedside to abstract the relevant information from the medical record, with corroboration from the patient's bedside nurse and treating team. When needed, the patient's cardiac anesthesiologist or perfusionist will be contacted to clarify.

Using a study laptop, all requisite information will be entered into a Microsoft Excel spreadsheet with the desired values listed on the left and each hour listed across the right. Data will be hand-entered into the spreadsheet by a member of the research team, and annotated as necessary to clarify discussions with relevant parties. These data will be double checked by a second member of the study team within 7 days.

Quality control methods

Quality in the data collected by the oxygen consumption monitor will be ensured by a self-test at startup according to the manufacturer's instructions. Further, anesthesiologist and respiratory care staff will be instructed to monitor for the degree of air leak from the respiratory system by calculating the difference between inspiratory and expiratory measured tidal volumes. If the airleak exceeds this value, air may be added to the tracheal tube cuff. We have shown that when this difference is <15%, VO_2 data are accurately measured in newborns.[24] Further, an absence of end-tidal CO_2 data will be used as a signal of an endotracheal tube disconnection and possible suctioning event. VO_2 measurements are known to be unstable for several minutes following suctioning[28], so we will exclude VO_2 data for 10 minutes following any ETT disconnect from analyses.

Data within the SVC monitoring probe will be ensured by an in vitro calibration prior to probe insertion. When ever the treating team sends a venous blood gas from the central venous line, the co-oximetry value will be entered into the machine and used to recalibrate the probe in real-time.

Quality in the transfer of data from the medical record to the spreadsheet will be ensured by an independent review of the primary data by a second member of the study team. Furthermore, when possible, the fields for data entry will contain 'Data Validation' functions (i.e. value will turn red if outside expected limits, and hard stops will be inserted for physiologically impossible values). Additionally, drop down lists will be utilized when possible to minimize data entry errors.

Data Analysis Plan
Patients will be divided into patients who do and do not experience PLOC. All variables will be normalized to hours prior to bypass, bypass time and hours post-bypass time, such that all data for a specific post-bypass time will be aligned between patients. All weight-dependent variables will be normalized to preoperative body weight. Using GraphPad Prism, each variable will be entered into a different column for analysis.

Simple analyses (e.g. mean, standard deviation, tests for normality) will be completed within GraphPad. With regards to the primary endpoint, VO_2 measurements will be analyzed for 120 minutes prior to a PLOC event in cases, and a randomly selected 120 minute period in controls. Values will be compared between cases and controls using generalized estimating equations (GEEs) to account for the correlation of multiple measurements within the same patient and to compare means between cases and controls. A post-hoc broken stick analysis will be used to determine the time prior to the event at which the VO_2 changed in each patient experiencing an event. Data for HLHS and dTGA patients will be pooled together.

More complex analyses will be completed by a collaborating company called Etiometry (including Dimitar Baranov, PhD and Evan Butler, PhD, co-investigators on this study), with whom the PI and others within the CICU have an established relationship. Deidentified information will be sent to the company, who will complete further analyses.

Power Calculations and Sample Size
The measured oxygen consumption in neonates following S1P has been described as 86±16 mL/min/m^2[22]. A sample size that includes 3 cardiac arrest events would allow us to detect a true decrease of 53 mL/min/m^2 in oxygen consumption with 90% power and a significance level of 0.05 (two tailed). Based on the significant change in VO_2 noted in the animal studies preceding cardiac arrest, we do not feel that this number is an unreasonable number. In order to collect 3 patients meeting the endpoint, we predict that we will require 20 patients undergoing S1P.

Risks and Discomforts
Because this is a prospective, observational study which we do not expect to change the standard of care, the risks associated with this study are really those of the standard

of care. The VO_2 measurements will be taken using an FDA-approved device which samples gas from the side of the tracheal tube of each patient. In reality, the adapter used by the study monitor is smaller and lighter than than used in our current capnographs, so the risk of accidental endotracheal tube removal should be the same or lower.

The second standard intervention used here which imposes risk is the insertion of an internal jugular venous catheter, which again is standard practice in newborns undergoing these procedures. The theoretical risks of this FDA approved device are no different from standard catheters, which include bleeding, infection and thrombosis. To address these, the staff within the CVP at BCH utilize an insertion bundle and antibiotic coated catheters, which will be a practice which is unchanged in this study. As per routine in the CICU, the catheters will be infused with a Heparin infusion at 10 Units/kg/hour through one of the two ports of the line, which will decrease any risk of thrombus formation. The catheters are additionally coated with AMC Thromboshield (a coating containing both Heparin and antimicrobials), which will further decrease the risks of both infection and thrombus formation.

Potential Benefits

Potential Direct Benefits

Because this is a prospective observational study, the measurements are not intended to change the standard of care by which these patients are treated. However, there are several possible direct benefits to patients:

- *Decrease in venous blood sampling*. It is possible that due to the indwelling oximeter that the care team will require fewer blood samples to be tested for SVC saturations. This could potentially decrease the blood loss associated with blood sampling and diminish the risk of infection (which is associated with the number of times a line is entered).
- *Improved assessments of Qp/Qs.* As discussed in the background section, the ratio of blood flow to the lungs to that of the body is a vitally important number in the care of patients with HLHS. In the CICU, it is common practice to make changes in patient management based on this value, although the value itself is quite often inaccurately assessed.[3] The primary unmeasured variable in the calculation of this ratio is the SVC saturation. The ability to constantly and accurately monitor this value, in combination with arterial saturations based on pulse oximetry, may vastly improve the quantification of the Qp/Qs ratio and better inform management decisions at the bedside for critically ill neonates.
- *Earlier recognition of circulatory failure*. Regardless of a patient's underlying anatomy, the difference in oxyhemoglobin saturation between a patients systemic arterial and venous circulations represents the adequacy of end organ oxygen delivery (reference Figure 1 above). It is possible that by continuously monitoring both the systemic arterial and venous oxyhemoglobin saturations (the former by pulse oximetry), that the treating team will be able to more rapidly identify evolving circulatory failure. There are many interventions which could be utilized

by the care team prior to PLOC which may improve patient outcomes as a result of and in response to this single factor.

Potential Indirect Benefits

This study has the potential to significantly improve the way that newborn patients (and others) are monitored in the postoperative period. Currently, the circulation of these patients are assessed indirectly, using surrogate measures (using cNIRS, and intermittent lactate and SVC saturations measurements) and vital signs. Because our definitive treatment for refractory circulatory failure is ECMO, and because ECMO itself can cause life-threatening complications, it is extremely challenging to determine which patients are at a higher risk of death or organ injury from inadequate DO_2 compared to the risks of these complications from ECMO. It is possible that if the primary hypothesis of the study, that critically ill patients in the CICU exhibit pathologically supply dependent oxygen consumption, that VO_2 monitoring could add significant, continuous, noninvasive information to the care of newborns during their highest risk period. For the short term, this could permit treating teams to measure the effects of their interventions on oxygen delivery (e.g. addition of inotropes, blood transfusions, clips on shunts) and inform these decisions. For the long-term, it is possible that VO_2 and continuous SVC saturation monitoring could inform a predictive algorithm for the sensitive and specific prediction of which patients suffer from recalcitrant circulatory insufficiency, those which may be at risk for PLOC, and who would benefit from ECMO support. If true, this would likely significantly improve the survival rate and neurologic outcomes of newborns with congenital heart disease.

Privacy and Confidentiality Provisions

Privacy Provisions

As mentioned above, patients will be identified by the PI or one of his designees by a regular, systematic review of the census and diagnosis list in the Cardiac Intensive Care Unit at Boston Children's Hospital. Therefore, patients will not be approached for consent unless they meet full inclusion criteria and their treating team assents. Only parents, who will be aware of their child's diagnosis of congenital heart disease, will be approached about the study. None of the patient's comorbidities will be discussed with the patient or family as part of this study.

Confidentiality Provisions

All data will be tracked using unique patient identifiers (UPI). Links between UPI and name and medical record number will be kept in a password-protected file on the PI's computer, and as a printed backup in the PI's locked office. Both of these will be destroyed following data analysis. All primary data will be saved on a hard drive maintained in the locked office of the PI. All data will be deidentified using the UPI as the only identifier. All data files will be password protected, and only study investigators will have access to this password. All files sent via email will be sent with encryption.

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List of Appendices

Oxy-CAHN Study

Oxygen consumption-based assessments of hemodynamics in neonates following congenital heart surgery

Enrollment Criteria

Preoperative HLHS (n = 20)
OR
d-TGA/IVS (n=20)

Assent of cardiac surgeon and cardiac intensivist
Parental consent

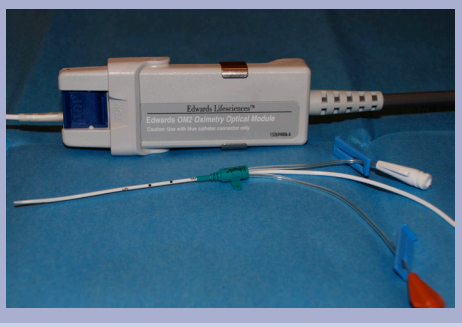
Cardiac OR

At first intubation*

-> Calibrate VO_2
-> Check ETT leak
-> Begin data collection

At CVL insertion*

-> In vitro calibration
-> Catheter insertion
-> Confirm position in SVC



Cardiac ICU

Daily collect:

-> Primary outcome (CPR, ECMO, death)
-> VO_2 and SVC saturations
-> Cardiac output and Qp/Qs
-> NIRS, lactate, UOP
-> Inotropes
-> Blood loss and transfusion
-> Sedatives, paralytics
-> Feedings
-> Vital signs

From S5 Collect™

From medical record and discussion with primary team

From T3 database

* Enrollment begins at either first intubation or central venous line insertion (whichever occurs first) and ends at first postoperative extubation or central venous line removal (whichever occurs last).