# *COMIRB Protocol*

**COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD**
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**Protocol #:** 18-2513

**Project Title:** Bedside Resources to Gauge Intravascular Volume Status in Hypovolemic Infants in the Operating Room

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## 1. Lay Language:

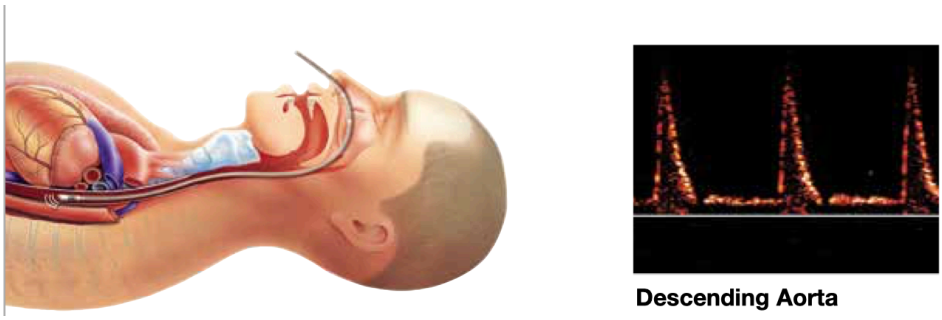
Predicting fluid responsiveness in the operating room is essential to guide balanced resuscitation. Aggressive resuscitation may lead to significant morbidities, such as intra-abdominal hypertension, pulmonary edema, difficulty with ventilator liberalization, and consequently increased mortality [1]. Alternatively, under resuscitation may lead to mal-perfusion and end-organ dysfunction.

A plethora of indices and tools have been studied and marketed to assess intravascular volume status with only a few proven reliable with reproducible results. Based on pre-fluid challenge values, several of these tools have been used to predict who may benefit from additional fluid (fluid responders). Alternatively, some of these tools have been used to distinguish fluid responders from non-responders based on changes in pre- and post-fluid challenge values. Among these tools, the pulmonary artery catheter provides measurements of both left and right heart pressures which can be applied to calculate the cardiac output (CO) and stroke volume (SV). Changes in these values (e.g. an increase in the stroke volume by 10%) between pre- and post-fluid challenge have been used to define fluid responders. This devise, however, is invasive with several significant risks, and therefore is rarely used in children. Echocardiography, on the other hand, is a non-invasive bedside study also used to assess CO and SV but is expensive and requires trained echosonagraphers for application. Further, because a transthoracic probe is required to obtain the images, application in the operating room is difficult as the chest is often in the operating field limiting access to the echosonagrapher. Lastly, the esophageal aortic blood flow device (CardioQ-EDM, Deltex Medical, Chichester, UK) has been found in multiple adult and pediatric studies to reliably distinguish fluid responders from non-responders intensive care unit (ICU) and operating room [2-6]. Much like an orogastric tube, this device is simply placed by a provider in the patient's esophagus and uses Doppler waveforms to measure aortic blood flow velocities (**Figure 1**). Variations in the amplitude of peak velocities has been shown to corelate with intravascular volume status[2-6]. Specifically, a change in the peak velocity by greater than 10% between pre- and post-fluid challenge values has

been shown to accurately distinguishes those who are fluid responsive from those who are not with similar accuracy to echocardiography and pulmonary artery catheter readings[7].

**Figure 1**

A B




Legend: A) Illustration of CardioQ-EDM position. In children age 15 years and younger, the device is introduced through the oral cavity. B) Correct placement confirmed by descending aortic waveform.

In recent years with continued technological advancements, there has been enthusiasm about less invasive, and in some cases, non-invasive, tools to gauge volume status. Among these, bedside ultrasonography (performed by providers rather than sonographers) is a common tool used to evaluate the inferior vena cava (IVC) collapsibility index (CI) has been shown to be a reliable tool in adults [8]. Another non-invasive device uses a photoplethysmoraphic probe (CipherOx-CRI) placed on a digit to calculate the compensatory reserve index (CRI), a marker of proximity to hemodynamic collapse [9]. Both IVC CI and CRI have been shown in multiple adult studies to predictive the need for volume expansion, but their utility in the pediatric population is unknown.

The goal if this proposed study is to employ the CardioQ-EDM probe to define fluid responders from non-responders among infants undergoing cranial vault reconstruction for craniosynostosis. After defining these two groups in this single arm prospective trial, we will compare the predictive utility of non-invasive devices such as the CipherOx-CRI and IVC CI to currently employed indices (heart rate, systolic blood pressure, urine output and pulse pressure variability) to gauge the need for additional fluid and ongoing resuscitation. If the CipherOx-CRI or IVC CI proved to be as predictive or better at predicting fluid responders, we hope to replace invasive arterial lines with non-invasive tools to guide resuscitation.

We chose this population for several reasons. First, CHCO performs approximately 50-70 of these cases a year making them a relatively accessible group. Second, these children are generally healthy

which will minimize physiologic confounders. Additionally, they are paralyzed, have normal respiratory compliance, and providers maintain normothermia all of which will minimizing confounders. Another unique benefit to this population is that these infants have been nil per os for several hours prior to surgery, putting them at risk for hypovolemia, and after induction, independent of the provider's assessment of intravascular volume status, they all receive a bolus of crystalloid (10mL/kg). This baseline data should provide sufficient data for analysis; but because these procedures are associated with significant blood loss and hypovolemia requiring aggressive resuscitation in the form of fluid or blood boluses[10], we plan to continue to collect pre- and post-bolus data with the hope to further validate the benefit of non-invasive tools such as the CipherOx-CRI and IVC CI in the setting of ongoing blood loss.

Aggregated data collected from the past five cases suggests that these infants lose approximately 100 mL of blood (17.2 mL/kg), receive 200 mL (37 mL/kg) of crystalloid and 75 mL (12.9 mL/kg) of blood (**Table 1**).

**Table 1: Previous Five Cranial Vault Reconstruction Procedures**

| Case Number | Age (months) | Weight (kg) | Blood Loss | | Infusion | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Crystalloid | | Colloid | Blood | |
| | | | (ml) | (ml/kg) | (mL) | (ml/kg) | (mL) | (mL) | (ml/kg) |
| 1 | 5 | 5.8 | 100 | 17.2 | 200 | 34.5 | 0 | 75 | 12.9 |
| 2 | 4 | 5.4 | 75 | 13.9 | 200 | 37.0 | 0 | 55 | 10.2 |
| 3 | 8 | 7.0 | 80 | 11.4 | 180 | 25.7 | 0 | 0 | 0 |
| 4 | 7 | 7.1 | 125 | 17.6 | 500 | 70.4 | 0 | 119 | 16.8 |
| 5 | 3 | 6.6 | 200 | 30.3 | 300 | 45.5 | 0 | 255 | 38.6 |
| Mean | 5.4 | 6.38 | 116 | 18.1 | 276 | 42.6 | 0 | 100.8 | 15.7 |
| Median | 5 | 6.6 | 100 | 17.2 | 200 | 37.0 | 0 | 75 | 12.9 |

As intravascular volume status is often difficult to assess clinically, we aim to determine the predictability of non-invasive devices to guide resuscitation. In this prospective observational study, we hope to identify:

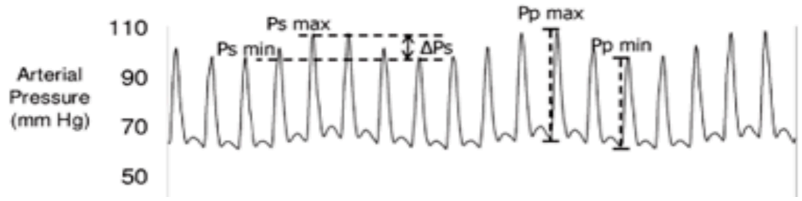
1. The proportion of children within the cohort who are fluid responsive based on CardioQ-EDM aortic blood flow velocity changes pre- and post-bolus,
2. The PPV, NPV, sensitivity, specificity, and optimal threshold for CRI, IVC CI, pulse pressure variability, stroke volume variability, heart rate, systolic blood pressure, and mean arterial pressures in predicting fluid responders as determined by CardioQ-EDM, and
3. Assess confounding variables that may influence the predictive utility of such devices

## 2. Background

Objective measures to guide resuscitation became mainstream with the introduction of the pulmonary artery catheter in 1970 [11]. Over the ensuing decades, several randomized control trials demonstrated that the use of pulmonary artery catheters did not incur a survival advantage. In fact, the complexity inherent in placing, operating, and interpreting data from this tool is not without risk. Thus, in large part, these invasive devises have fallen out of favor [12-14]. There has since been a focus on developing minimally invasive and non-invasive tools to gauge intravascular volume status in order to accurately direct resuscitation.

Several of these techniques rely on cardiopulmonary interactions with the cyclic variations of intra-thoracic pressure produced by ventilation. In a mechanically ventilated patient, changes in intra-thoracic pressures are transmitted to the right ventricle with increased pressure during inspiration and decreased pressure during exhalation. In patients who are intravascularly deplete, these pressure shifts lead to larger variations in measured parameters such as pulse pressure, IVC collapsibility, and plethysmography throughout the respiratory cycle. **Figure 2** describes the variation in pulse pressure which is represented by ΔPs. Plethysmography variation and CI are derived in a similar fashion using corresponding waveforms with the notion that more variation correlates with less intravascular volume.

**Figure 2**




$Pp_{min}$, minimal arterial pulse pressure; $Pp_{max}$, maximal arterial pulse pressure; $Ps_{min}$, minimal arterial systolic pressure; $Ps_{max}$, maximal arterial systolic pressure; ΔPs, pulse pressure variability. From Vasodilation increases pulse pressure variation, mimicking hypovolemic status in rabbits. Westphal GA, Goncalves AR, Bedin A et al., 2018, *Clinics[15]*.

Tools and indices available to measure intravascular volume status are numerous with the most frequent utilized ones described in **Table 2**. These indices range from simply measuring the systolic blood pressure to using computer generated algorithms in order to calculate a CRI. This armamentarium has vast applicability, but the predictive utility is variable, influenced by several confounders, and must be applied in the appropriate clinical setting.

**Table 2: Intravascular Volume Status Measurements**

| **INVASIVE DEVICES** | |
|---|---|
| SWAN-GANZ CATHETER | CO, SVR, SV, LVEDAI, GEDVI, CVP, PCWP |
| CENTRAL VENOUS CATHETERS | CVP, $SvO_2$, $\Delta pCO_2$ |
| ARTERIAL LINES | PPV, SVV, SPV |
| ESOPHAGEAL DOPPLER | ΔVpeak, SV, CO, ABF |
| CAPNOMETER | $\Delta ETCO_2$ |
| | |
| **NON-INVASIVE** | |
| VITAL SIGNS | HR, SBP |
| PLETHYSMOGRAPHY | Plethysmography variation index |
| ULTRASONOGRAPHY | IVC CI |
| ECHOCARDIOGRAM | CO, SV |
| COMPENSATORY RESERVE INDEX | CRI |

CO – cardiac output, SVR – systemic vascular resistance, SV – stroke volume, LV – left ventricular end-diastolic area index, GEDVI – global end-diastolic volume increase, CVP – central venous pressure, PCWP – pulmonary capillary wedge pressure, $SvO_2$ – mixed venous oxygen saturation, ΔpCO2 – delta partial pressure of carbon dioxide, PPV – pulse pressure variation, SVV – stroke volume variation, SPV – systolic pressure variation, ΔVpeak – delta aortic blood flow peak velocity, ABF - aortic blood flow, $\Delta ETCO_2$ – delta end-tidal carbon dioxide level, HR – heart rate, SBP – systolic blood pressure, IVC – inferior vena cava, CI – collapsibility index, CO – cardiac, CRI – compensatory reserve index

While large series have evaluated the predictive utility of various devices in adults, reports appraising tools used to assess fluid responsiveness in children are limited with heterogeneous findings [16]. A systematic review by Gan et al. published in 2013 reviewed 12 pediatric studies that, in total, evaluated 24 markers of fluid responsiveness in 439 children. The only variable that was repeatedly found predictive of fluid responsiveness and distinguish fluid responders from non-responders was variation in aortic blood flow peak velocity (ΔVPeak) obtained from the CardioQ-EDM. Not only has this tool been shown to predict those who will benefit from additional fluid, but, based on changes in pre- and post- fluid ΔVPeak, in it has been shown to accurately distinguish fluid responders from non-responders [7].

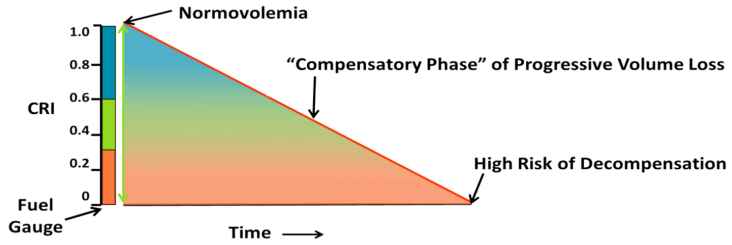
In adults, the esophageal CardioQ-EDM has been used both in the operating room and ICU. Among adult trauma patients admitted to the ICU, CardioQ-EDM has been used to guide resuscitation and shown to decrease infection complications as well as reduce ICU and hospital length of stay [17]. In children, increased enthusiasm in recent years has led to a number of small clinical trials most of which have been performed in Europe. In a metanalysis published in 2016 included six studies and 163 ventilated children, comparing CardioQ-EDM to echocardiography the authors concluded that the area under the summary receiver operating characteristic curve to distinguish responders from

non-responders for ΔVPeak was 0.94 [18]. While the optimal ΔVPeak varied from 7-20% among studies, one of the larger series using a ΔVPeak of 10% as a threshold found the sensitivity and specificity to be 100% in distinguishing fluid responders based on aortic velocity–time integrals identified by transthoracic echocardiogram [7]. Based on these results, we plan to define fluid responders as those who have >10% ΔVPeak between pre- and post-fluid challenge.

Bedside evaluation of the IVC to calculate the CI is a commonly used tool in adults [19, 20]. It serves as a surrogate to measure preload variation induced by mechanical ventilation. The technique requires limited ultrasonographic experience often at the critical care or anesthesia fellow level. In pediatrics, the predictive utility of IVC CI has only been evaluated in small series with conflicting results [21].

The CRI is another non-invasive devise using a photoplethysmoraphic probe (CipherOx-CRI) placed on the index finger. Based on data gathered from the probe, a computer-generated algorithm is then used to calculate a number between zero and one, referred to the CRI (**Figure 3**) [22]. The CRI correlates to one's intravascular volume status and proximity to hemodynamic collapse [23].

**Figure 3**




Legend: CRI, compensatory reserve index. CRI=1 is normovolemia and CRI=0 is the point at which the patient is at highest risk for hemodynamic decompensation.

Confounders that can influence dynamic measurements must also be considered. For instance, cardiac arrhythmias, small tidal volumes, spontaneous respiration, and high positive end-expiratory pressure have been found to decrease the predictive utility of pulse pressure variability and IVC CI [24-26]. Thus, it is paramount to use and apply these measurements in the appropriate clinical setting. Presumably, the influence confounding variables have on the predictive utility of these indices in children is similar to that of adults, however, comparative analyses have not been performed. Thus, when interpreted in the appropriate clinical context, these minimally and non-invasive devices are tools available to guide a balanced fluid resuscitation; however, while small series exist in various pediatric populations, validation is necessary in order to apply these tools in hypovolemic children with significant blood loss.

While numerous tools are available to guide resuscitation, one potential benefit of this project is to validate the use of CipherOx-CRI in this cohort. If CRI proves to be a valuable predictor of intravascular volume status and the need for volume expansion, this could negate the need for arterial line placement which is time consuming, invasive, and associated with complications such as arterial thrombosis. Furthermore, after validation in this cohort, additional studies could be performed in other groups of children at risk for hemorrhagic shock in the hopes to guide ongoing resuscitation accurately without the need for invasive devices.

**3. Specific Aims and Hypotheses:**

Aim I: Among infants undergoing cranial vault reconstruction for craniosynostosis, we aim to determine the proportion who respond to clinically administered fluid or blood products defined by pre- and post-fluid challenge EDM ΔVPeak >10%.

Hypothesis Ia: We hypothesize that approximately half of the cohort will be fluid responsive defined by ΔVPeak by > 10% after a 10 mL/kg fluid bolus is administered immediately following induction. Although this is a prediction, it is based on previous published reports suggesting a relatively even distribution among patients who clinicians believe need volume expansion. Additionally, because these children have a mean weight of 6.4 kg and will have been nil per os for several hours prior to surgery, they are at risk for intravascular volume depletion even prior to blood loss.

Hypothesis Ib: Because clinicians use pulse pressure variability, heart rate, systolic blood pressure, urine output, and blood loss to gauge need for ongoing resuscitation (either crystalloid, colloid, or blood), we suspect that more than half of subsequent fluid challenges will be given to infants who are fluid responsive (defined by a pre- and post-bolus ΔVPeak of > 10%).

Aim II: To determine the PPV, NPV, sensitivity, specificity, and optimal threshold for CRI, collapsibility index, pulse pressure variability, stroke volume variability, heart rate, systolic blood pressure, and mean arterial pressure as tools to predict fluid responsiveness using pre- and post-fluid challenge EDM ΔVPeak >10% to define fluid responders.

Hypothesis II: CRI and collapsibility index will reliably predict fluid responsive patients with an approximate area under the receiver operating characteristic curve (AUROC) of 0.9 while other indices will have a lower predictive accuracy.

Aim III: Evaluate confounding variables that may influence predictive measures outlined in Aim II.

Hypothesis III: Confounding variables that may decrease the predictive accuracy of indices described in Aim II include spontaneous breathing over the ventilator, minimal blood loss, and hypothermia

**4. Materials and Methods:**

***4.1 Pre-trial Training***

1) Prior to patient enrollment, the principle investigator (PI) and two co-investigators will be trained by a certified ultrasonographer regarding how to measure the IVC CI. After participating in a one-hour skills lab, the PI and co-investigators will be evaluated for competency and reproducibility. If deemed incompetent, remediation will be required prior to the start of the trial. Additionally, we will confirm inter-observer reliability between co-investigators to assure measurement reliability.

2) The PI and Co-investigators (Drs. Shahi or Phillips) will be trained in the appropriate placement and operation of the CardioQ-EDM probe and monitor by a manufacturer representative. Given the PI's extensive experience with both nasal and oroesophogeal device placement (see below), after the manufacturer representative confirms competency with appropriate probe positioning, he will be responsible for all probes placed. Prior to enrolling patients in the study, a manufacturer representative will provide a live demonstration in a child undergoing cranial vault reconstruction after informed consent.

***4.2 Materials Necessary***

1. Esophageal aortic Doppler (CardioQ-EDM) probe = 30 provided by Deltex Medical

2. CardioQ-EDM monitor = 2 provided by Deltex Medical
3. Bedside Ultrasound = 2 machines are available in the operating room at all times
4. CipherOx CRI – Provided by Division of Pediatric Surgery

### *4.3 Patient recruitment*

Patients will be identified by the PI based on communication with the craniosynostosis clinic team. Parents/guardians of eligible candidates will be approached by a study team member at their pre-operative appointment or on the day of surgery for voluntary participation. If recruitment is insufficient (<70%), a $20 gift card will be used as incentive for study participation. Funding will be provided by the division of pediatric surgery if this is necessary.

**4.3.1 Population:** Children older than 3 months and younger than 2 years of age who undergo cranial vault reconstruction in the supine position will be included. Children with associated syndromes will be included as long as they do not have known underlying cardiac abnormalities. Consent will be translated into Spanish as well for those in whom it is indicated.

**4.3.2 Exclusion Criteria:** Children with known underlying cardiac anomalies or cardiac arrhythmias, infants younger 3 months of age or greater than 2 years of age. In addition, children weighing less than 3 kg will be excluded at the recommendation of the manufacturer. While vasopressor (epinephrine, norepinephrine, and/or vasopressin) support is not a contraindication, fluid boluses administered during dosage adjustments will be excluded from analysis. Patients who are placed in the prone position for surgery will also be excluded given the difficulty with obtaining a window to measure the IVC CI and possible effect on reported measurements. Additionally, if abnormal anatomy is discovered while assessing the IVC, these children will also be excluded from analysis.

### *4.4 Definitions*

- *Bolus* – 10 - 20 ml/kg fluid (isotonic crystalloid, colloid, or blood product) up to 1 L and given within a 10 minutes period
- *Fluid responders* – Children who have a pre- and post-fluid challenge ΔVPeak > 10% calculated using the equation ($\Delta VPeak_{pre} = (VPeakmax_{pre} - VPeakmin_{pre})/$

[(Vpeakmean$_{pre}$]) - ($\Delta$VPeak$_{post}$ = (VPeakmax$_{post}$ – VPeakmin$_{post}$)/ [(Vpeakmean$_{post}$]) x 100

- *Multiple fluid challenges* – If more than one fluid bolus is administered at least 30 minutes apart, they will be reported as individual events
- *Pre-bolus measurements* – Hemodynamic measurements will be calculated or recorded three times thirty seconds apart and averaged just before a bolus is administered. Cine loops from IVC measurements will be recorded three times, thirty seconds apart for post-hoc CI calculation. Peak aortic velocity and CRI will be recorded on the EDM monitor and averaged over 90 seconds.
- *Post-bolus measurements* - Hemodynamic measurements will be calculated or recorded three times and averaged five minutes after a bolus is completed. These measurements will be time and repeated in an identical fashion to pre-bolus measurements.

### *4.5 Decision for volume expansion*

All children receive a 10 ml/kg crystalloid bolus immediately after induction. The need/decision for a fluid bolus will be determined by the anesthesiologist based on clinical judgement. Currently, the anesthesiologist places an arterial line at the beginning of the case and using pulse pressure variability, HR, SBP, MAP, urine output, and blood loss determines whether or not a fluid or blood bolus is appropriate. Data collected from the CardioQ-EDM, CipherOx-CRI, and bedside ultrasound will not be provided to the care team.

### *4.6 Data Acquisition*

If consent is obtained, a CardioQ-EDM probe will be placed on the day of surgery after induction of general anesthesia. One of the investigators will be present in the operating room for the duration of surgery to perform study procedures (PI or Co-investigators (Drs. Shahi or Phillips) to place all CardioQ-EDM probes) and gather study data. The anesthesiologist will inform the investigator of plans to provide a fluid or blood bolus per clinical judgement in addition to the protocolized 10 ml/kg bolus provided after induction. While the anesthesiologist is preparing to administer volume expansion, a co-investigator will collect pre-fluid bolus data. Administration of fluid will not be delayed for any reason, including performance of study measurements. Measurements will be recorded for data analysis at the completion of the trial (see below). Additionally, a CipherOx-CRI probe will be placed on the patient's index finger (again, recorded data will be interpreted post hoc) and a bedside ultrasound will be performed by either the PI or one of two co-investigators to measure the IVC CI. The IVC CI will be visualized through a sub-xyphoid window. The ultrasound

indicator will be aimed at the child's left flank. Once the right atrium is identified, the ultrasound probe will be turned 90 degrees counterclockwise so the indicator is directed at the head. The best way to evaluate the IVC diameter through the respiratory cycle is to use M mode. After positioning the probe appropriately in order to visualize the IVC 2 cm inferior to the cavo-atrial junction, the M mode will be activated to measure variation in the IVC diameter with respiration. Ultrasound cine-loops will be recorded, and CI will be calculated post-hoc. Data will be recorded on the *Data Collection Form* for each fluid bolus administered. The PI and co-investigators will manage all aspects of investigational devices.

**Day of Surgery Step-by-step Description:**

1. While the anesthesiologist intubates and places an arterial-line, the CardioQ-EDM monitor, CipherOx-CRI device, and U/S will be set up
2. After positioning the patient for surgery, the CardioQ-EDM device will be placed through the mouth into the esophagus by the PI or Co-investigators (Drs. Shahi or Phillips) and the aortic Doppler waveform will be confirmed. Additionally, the CipherOx-CRI finger probe will be placed, and a baseline IVC CI will be measured and recorded.
3. Baseline values and measurements (included in **Table 3**) will be recorded. Additionally, the baseline ΔVPeak and CRI will be recorded.
4. A protocolized 10 mg/kg crystalloid fluid bolus will be administered
5. Two minutes after the bolus has completed, repeat EDM and CRI values will be recordings and a repeat abdominal ultrasound to measure the IVC CI will be obtained.
6. If an additional fluid bolus or blood transfusion is administered during the remainder of the procedure, steps 3 and 5 will be repeated.

***4.6.1 Demographic Data:*** Age, weight, height, body mass index (BMI), gender, and ethnicity will be collected from medical records.

***4.6.2 Ventilator Data:*** pressure or volume control, tidal volume (ml/kg) and peak end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), and spontaneously breathing.

***4.6.3 CardioQ-EDM Data:*** Based on a validated internal nomogram derived from the child's age, height, and weight[27], peak velocities will be obtained from the Cardio-EDM monitor.

***4.6.4 Fluid Data/Vasopressor Administration:*** Number, time, type, and volume of fluid/blood administered will be recorded in real time. Vasopressor agent, dose, and time administered will also be reported.

***4.6.5 Waveform/Vital Data:*** As it is currently not possible to extract waveform data from the operating room monitors, we will record data in real time. Values listed below will be reported on an excel spreadsheet.

**Parameters to measure:**

All parameters will be measured x 3 with 30 seconds between each measurement and averaged

- Systolic blood pressure (measured by arterial line)
- Mean arterial pressure (calculated from arterial line)
- Heart rate
- Pulse pressure variability (measured by arterial line) = acquired from arterial line
- Stroke volume variability – acquired from arterial line
- ΔVpeak = (VPeakmax – VPeakmin)/ [(Vpeakmean] x 100
- Compensatory reserve index – algorithmically generated
- Inferior vena cava collapsibility index = Maximum diameter (expiration) – minimum diameter (inspiration)/maximum diameter (expiration) in M mode

**4.7 Data Blinding:**

Reporting bias will be minimized by limiting interactions between the study team and OR team. Furthermore, as all children receive a bolus prior to incision, independent of available indices used to assess intravascular volume status, bias should be minimized for this fluid bolus. As these devices are experimental in this patient population, anesthesiologists will be blinded to hemodynamic data generated by the CardioQ-EDM, bedside ultrasound, and CipherOx CRI. If data is needed in an emergent setting, the subject will be excluded from analysis. Although recorded measurements from the Cardio-Q EDM monitor will be visible to the study team, IVC measurements will be stored and calculated post-hoc by a co-investigator blinded to whether or not the subject is or is not fluid responsive. Additionally, a trained statistician not involved in data collection will be paid for analysis. It should also be noted at Dr. Steven Moulton is a paid officer of CipherOx but will not be involved in the data collection and analysis.

***4.8 Data Analysis***

Univariate comparisons between various measures will be compared between the fluid responder and non-responder groups using t-tests or Fisher's exact test for continuous and categorical measures, respectively. Area under the curve will be calculated for CI and CRI using both simple logistic regression models including no confounders and multiple logistic regression models including confounders. Confounders will be identified for inclusion in the multiple logistic regression models by calculating the univariate association with the gold standard (using a $p<0.10$ threshold). These adjusted models will be used to verify thresholds for classification using CI and CRI which will then be applied to calculate classification summary measures (e.g., PPV, NPV, sensitivity, and specificity). Data analysis will be performed by a biostatistician funded by the Division of Pediatric Surgery using R and SAS statistical software programs.

### *4.9 Risk, Safety, and Indications/Contraindications*

Both the Deltex Medical CardioQ-EDM (Deltex Medical Limited; K172457; June 28, 2018), and the CipherOx CRI, (Flashback Technologies, Inc.; K173929; July 24, 2018), have been cleared through Class II/Traditional 510(k)s.

The CardioQ-EDM has been used in over 400,000 patients worldwide. To date, there have been no serious adverse events associated with EDM. Extrapolating data from nasogastric tube and transesophageal echocardiography probe placement, the incidence of esophageal perforation is exceedingly low and only described in case reports and small case series. Nonetheless, the risk of esophageal perforation will be discussed during the informed consent process. The co-investigator in the operating room will be responsible for reporting any adverse events to the PI. In the event of an adverse event, the PI will fully disclose details to the participants family, COMIRB, Children's Hospital Research Institute, and Deltex Medical.

To minimize risk associated with CardioQ-EDM placement, the PI or Co-investigators (Drs. Shahi or Phillips) who all have experience placing similar objects will place the device by applying jaw thrust in the standard fashion. Proper positioning of the device will be confirmed by Doppler waveform, negating the need for radiographic confirmation. Specific pediatric CardioQ-EDM probes (KDP72) which are indicated in children age 15 and younger will be placed through the oral cavity. Although the device has not been used at CHCO previously, the insertion is identical to an orogastric tube placement and thus the investigators do not believe that a bioengineering review is necessary.

One additional risk is the potential for extubation with probe manipulation. To minimize this risk, probes will be placed while the anesthesiologist maintains the airway. If at any point during the case, the probe becomes mal-positioned, no repositioning will be performed, and the study is terminated for this individual in an effort to avoid inadvertent extubation. Furthermore, the probe

will remain in place until the time of extubation to again minimize the risk of inadvertent extubation.

The CipherOx-CRI probe was cleared by the FDA for patients with a finger thickness of 0.3 to 1 inch. There were no warnings, precautions or contraindications in the product brochure.

### *4.9.1 CardioQ-EDM Details*

- The Deltex Medical Doppler KDP72 probe is for use in patients aged 15 years or younger for up to 72 hours.
- The KDP probe is 28 in (72 cm) long and has maximum usage time which is defined on the probe packaging.
- It is only approved for ORAL placement into the esophagus of a single patient over 5.5 lb. (2.5 kg) in weight.
- The patient should be under full sedation or general anesthesia.
- The probe shaft has six depth markers visible through the transparent cover starting at 6 in (15 cm) through to 16 in (40 cm) incrementing in steps of 2 in (5 cm). These markers act as a guide to facilitate correct probe placement.
- Nasal placement of any probes in patients aged 15 years or younger is not approved nor is usage of the CardioQ-EDM for patients below 5.5 lb. (2.5 kg) in weight.

### *4.9.2 CardioQ-EDM Contraindications*

- Doppler probes (DP240 and I2n) should not be placed in patients under 16 years of age. We will be using the KDP72 probe
- Do not use where nasal injuries are apparent or may have occurred.
- Do not use where nasal polyps exist.
- Do not use where there are circumstances of facial trauma.
- Do not use where there is a risk of brain injury.
- Do not use in patients undergoing intra-aortic balloon pumping.
- Do not use with carcinoma of the pharynx, larynx or esophagus.
- Do not use with aneurysms of the thoracic aorta.
- Do not use with tissue necrosis of the esophagus or nasal passage.
- Do not use in close proximity to laser surgery.
- Do not use in patients with pharyngo-oesophago-gastric pathology and/or severe bleeding diatheses.

**5. Specific Aims:**

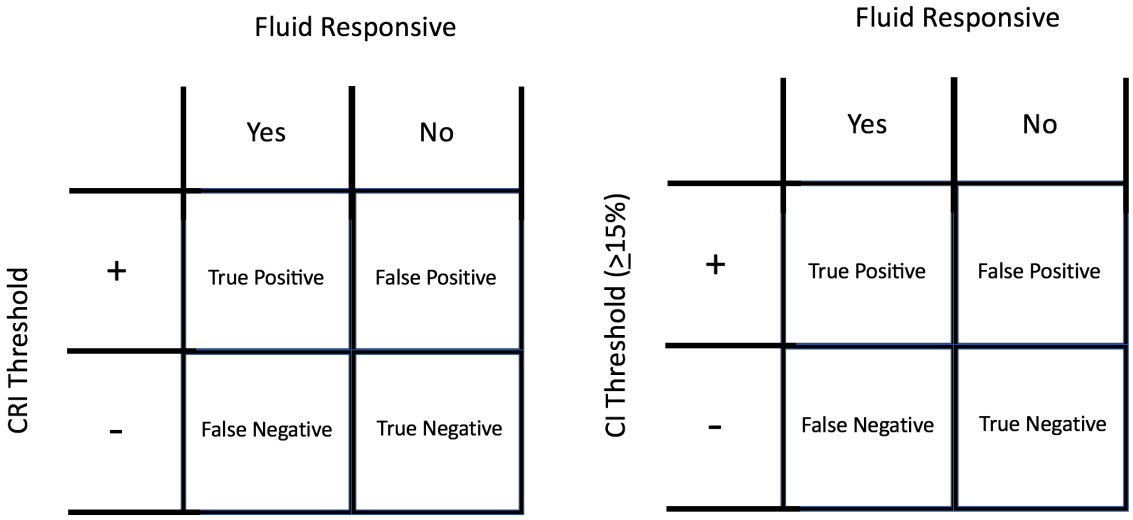
***Aim I: Define fluid responders based on aortic ΔVpeak:*** Among infants undergoing cranial vault reconstruction for craniosynostosis, we aim to determine the proportion who respond to clinically administered fluid or blood products defined by pre- and post-fluid challenge EDM ΔVPeak >10%.

**Mock-up Table 1: Demographics of Responders and Non-Responders to Initial 10 mL/kg bolus prior to surgical incision**

| Variable | Responders | Non-Responders | P-value |
|---|---|---|---|
| Demographics | | | |
| Age | | | |
| Weight | | | |
| Height | | | |
| BMI | | | |
| Gender | | | |
| Ethnicity | | | |
| Duration of NPO status | | | |
| Associated syndrome | | | |

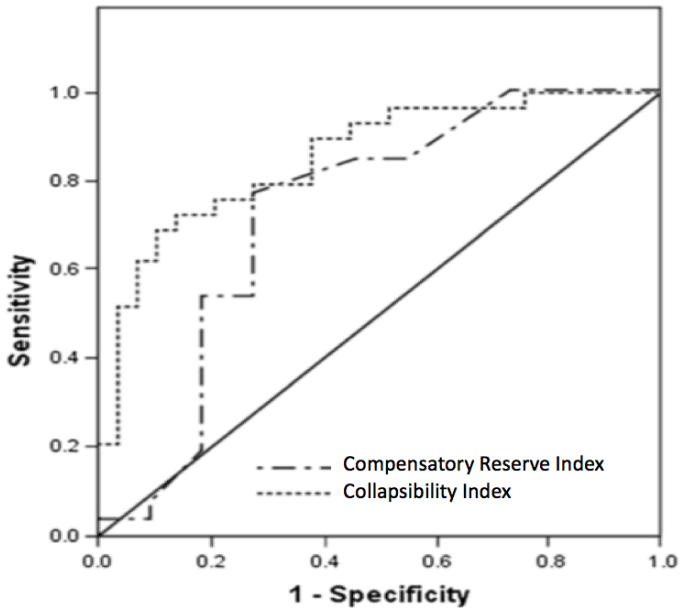
Legend: BMI, body mass index; npo, nil per os

***Aim II: Calculate the PPV, NPV, sensitivity, specificity, and optimal threshold for CRI and collapsibility index as tools to prediction fluid responder***




Performance will also be calculated for heart rate, systolic blood pressure, mean arterial pressure, pulse pressure variability and stroke volume variability. Two separate analyses will be performed – one for the 10 ml/kg protocolized bolus provided immediately after induction and one accounting for all boluses provided.

**Mock-up Figure**




**Mock-up Table 2 – Performance at predicting fluid responsiveness**

| Variable | Correlation (r) | AUC |
|---|---|---|
| IVC CI | | |
| CRI | | |
| SBP | | |
| PPV | | |
| SVV | | |
| MAP | | |
| HR | | |

***Aim III: Evaluate confounding variables that may influence CRI or collapsibility index***

| Variable | Scale of Measurement | Data Point Location | Analysis Method |
|---|---|---|---|
| **Outcome Variable** | | | |
| IVC CI, CRI, PPV, SVV, HR, SBP, MAP AUROC | Interval | Pre-bolus measurements | |
| **Confounding Variables** | | | |
| Age | Interval | Demographics | |
| Weight | Interval | Demographics | |
| BMI | Interval | Demographics | |
| Gender | Dichotomous | Demographics | |
| Ethnicity | Ordinal | Demographics | |
| Associated syndrome | Dichotomous | Demographics | Multivariable |
| Preoperative Hemoglobin | Interval | Preop results | Linear |
| Duration of NPO status | Interval | Anesthesia Rec | Regression |
| Core temperature at time of bolus | Interval | Anesthesia Rec | |
| Paralysis provided (Y/N) | Dichotomous | Anesthesia Rec | |
| Blood transfusion (Y/N) | Dichotomous | Anesthesia Rec | |
| Total blood volume | Interval Interval | Anesthesia Rec | |
| Total Crystalloid | Interval | Anesthesia Rec | |
| Total Colloid | Dichotomous | Anesthesia Rec | |
| Vasopressor requirement | Interval | Anesthesia Rec | |
| Total amount of vasopressor | | Anesthesia Rec | |
| Ventilation | Interval | | |
| Tidal volume | Interval | Ventilator | |
| PEEP | Interval | Ventilator | |
| PIP | Dichotomous | Ventilator | |
| Spontaneous breaths | | Ventilator | |

Figure or Table will depend on results found. If neither of the outcome variables are affected by the confounding variables may only report this finding in the text.

Two separate analyses will be performed – one for the 10 ml/kg protocolized bolus provided immediately after induction and one accounting for all boluses provided.

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