Cerebral Oximetry in Management of Post CArdiaC ArresT (COMPACT): A Pilot Randomized Controlled Trial

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I. Background

A. Hypoxic-Ischemic Brain Injury Outcomes

Persistent coma following resuscitation from a cardiac arrest is a common indication for admission to an intensive care unit (ICU) [1]. Across Canada, there are more than 60,000 out-of-hospital cardiac arrests per year [2].

Many patients with hypoxic-ischemic brain injury (HIBI) do not awaken from coma and eventually have life-sustaining treatments withdrawn because of a poor long-term neurologic prognosis. Some survivors are left with permanent physical and cognitive disabilities [3-5]. Provincial data from 2012-2019 revealed that hospital mortality for HIBI patients with an initial Glasgow Coma Scale (GCS) score of 8 or less was almost 70% and only 25% were discharged home or to a rehabilitation facility. Better treatments for post-arrest patients are therefore urgently needed.

B. Hypoxic-Ischemic Brain Injury Pathophysiology

Neurovascular units (neurons, glia, endothelium, blood brain barrier) are highly vulnerable to oxygen (O_2) deprivation [6]. Lack of cerebral blood flow (CBF) and O_2 delivery during periods of "no flow" (without CPR) and "low flow" (with CPR) results in ischemic depolarization within minutes [7-8][7-8]. If not rapidly reversed, neuronal death ensues [9].

After ROSC, there is a cascade of events in brain tissue that perpetuates HIBI. Microthrombosis, endothelial edema, and neutrophil recruitment in capillaries and venules, together with loss of CBF autoregulation contribute to persistent regional hypoperfusion [10-12]. Breakdown of the blood-brain barrier causes vasogenic edema, which impairs diffusion of O_2 [13]. Excitotoxicity and, in some cases, seizures increase energy demand. In combination, these factors cause imbalance of O_2 supply and demand, with consequent secondary brain injury. This post-arrest "dysregulation phase" may last for hours or even days [6].

C. Treatment of Inadequate Oxygen Delivery

Cerebral O_2 delivery can be augmented through measures that increase cerebral blood flow (CBF) or arterial oxygen content. Methods to raise CBF include augmenting cardiac output by administering fluids or inotropes, increasing mean arterial pressure (MAP) with vasopressors, lowering the head of the bed, and inducing cerebral vasodilatation by targeting a higher partial pressure of carbon dioxide (PCO_2). Arterial O_2 content can be raised by increasing arterial oxygen saturation, transfusing red blood cells, or maintaining a higher partial pressure of oxygen (PO_2) to increase the amount of O_2 dissolved in blood.

Studies assessing the efficacy of higher MAP, PO_2, and PCO_2 have failed to show any therapeutic benefit in management of post-cardiac arrest patients [14-16]. However, these interventions were applied

irrespective of whether cerebral O_2 delivery was impaired. Augmenting O_2 delivery can only be beneficial if it is first reduced.

D. Detection of Inadequate Oxygen Delivery

A more targeted approach would be for physiological goals to be guided by neuromonitoring. Invasive brain tissue oxygen tension or cerebral blood flow monitors are rarely inserted in post-arrest patients [17]. Patients where the arrest is due to cardiac etiologies often require anti-platelet therapy or anticoagulation, which contraindicate placement of intracranial devices. Jugular bulb oxygen saturation ($S_{jv}O_2$) is measured at some centers but requires placement of a retrograde catheter into the internal jugular vein, maintained at approximately the level of C1 vertebra [18]. Most cardiac ICUs to not have the equipment or expertise to measure $S_{jv}O_2$ continuously.

In contrast, cerebral oximetry is a safe, non-invasive, and user-friendly modality that utilizes near infrared spectroscopy (NIRS) to assess hemoglobin oxygen saturation in the frontal lobes. Probes are applied to the forehead and emit light with wavelength in the near infrared spectrum (650-1000 nm), to which bone is relatively transparent. Light is absorbed by chromophores, including hemoglobin, according to the Beer-Lambert principle, whereby absorption is greater with a higher concentration of a substance and increasing distance. Reflected light is measured at the scalp by sensors in the probe. The light absorption spectrum differs for oxy- and deoxyhemoglobin. By emitting light of multiple wavelengths and measuring the reflection, commercially available oximeters can estimate hemoglobin oxygen saturation. Depth is controlled through the distance between light emitters and detectors. Cerebral oximetry assesses mainly venous blood, such that regional oxygen saturation (rSO_2) is usually 60-75% [19-20]. Low pre-operative rSO_2 and intra-operative desaturation during cardiac surgery have been associated with post-operative cognitive impairment [21-23]. Desaturation during extracorporeal life-support is predictive of cerebral ischemia [24]. Higher rSO_2 during cardiopulmonary resuscitation has been associated with a greater chance of ROSC [25].

E. Relationship Between rSO_2 and Outcome in Post-Arrest Patients

We conducted a systematic review of 16 studies of continuous cerebral oximetry from 0-48 hours post-arrest [26]. Patients with poor neurologic outcomes had lower rSO_2 values, and a wider standard deviation, suggesting that they were more prone to both higher (reduced O_2 utilization) and lower (reduced O_2 delivery) rSO_2. Differences were modest and there was considerable overlap between groups. These findings support the hypothesis that raising rSO_2 could improve outcomes following cardiac arrest. Mean rSO_2 during the initial 24 hours post arrest was generally about 60-62% (standard deviation 55-67%) among patients with poor outcome and about 64-66% (standard deviation 60-70%) among patients with favourable outcomes.

There were, however, numerous limitations to these findings, including substantial heterogeneity between studies, variable timepoints where rSO_2 was reported, and lack of clinician blinding. Low rSO_2 was associated with longer cardiac arrest duration, suggesting that it may also be a measure of severity

of brain injury, rather than a variable that should be corrected. Furthermore, low rSO_2 may be a marker of poor systemic perfusion, rather than indicating only inadequate cerebral oxygen delivery. There may be variability in rSO_2 based on age, sex, skin pigmentation, and skull thickness [27-29].

F. Why a Clinical Trial is Needed

There are no previous clinical trials of individualized neuromonitoring-guided resuscitation in patients with HIBI. Comparable research, using invasive neuromonitoring, has shown promise in patients with traumatic brain injury and is being evaluated in multi-center trials. Before a larger multi-center trial can be justified, feasibility, safety and proof of concept should first be established. This will allow us to assess and refine the management protocol.

II. Objectives

(1) Proof of Concept:

A. Assess the efficacy of a treatment protocol in avoiding and correcting cerebral hypoxia (rSO_2 < 60%).
B. Assess the efficacy of cerebral-oximetry guided treatment in attenuating secondary brain injury (assessed using serum biomarkers of brain injury).

(2) Assess feasibility (consent, enrolment and compliance) and safety (adverse events) of the treatment protocol to help plan a future larger multi-center clinical trial.

III. Study Design

This will be a prospective randomized controlled trial with blinded allocation in a 1:1 ratio to either standard care or a treatment protocol guided by cerebral oximetry. The study will commence in the Foothills Medical Center multi-system ICU, a unit with 34 beds. After enrollment of at least 2 patients, the study will expand to the Foothills Medical Center cardiac ICU (CICU). Patients admitted to the multi-system ICU usually have cardiac arrests caused by non-cardiac conditions, most often with non-shockable rhythms. Patients admitted to the CICU usually have cardiac arrests attributable to cardiac etiologies, and commonly involve shockable rhythms. It is anticipated that enrolment will occur over about 2 years.

IV. Patient Population

The target population is patients resuscitated from cardiac arrest that are at risk of HIBI.

Patients will be included if they meet each of the following criteria:

(1) Age 18 years old or older.
(2) Resuscitated from cardiac arrest lasting 5 minutes or more.
(3) Comatose (GCS $\leq$ 8) following ROSC.

The purpose of these criteria is to avoid enrolling patients that are at low risk of significant HIBI. It is acknowledged that the initial neurological examination of post-arrest patients may be confounded by sedatives. Inclusion criterion 3 is to avoid enrolling patients that regain consciousness immediately following ROSC.

Patients will be excluded if they meet any of the following criteria:

(1) The etiology of the cardiac arrest was any form of brain injury (traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke or central nervous system infection).
(2) The patient cannot be enrolled within 6 hours of ROSC.
(3) The patient is unsupportable. This will be at the discretion of the attending physician and the principal investigator (or designate) and will generally consist of patients in whom conventional physiological goals (MAP $\geq$ 60 mmHg and arterial oxygen saturation $\geq$ 90%) cannot be consistently achieved
(4) A CT scan (if performed) demonstrates diffuse loss of grey-white differentiation involving both the cortex and basal ganglia. Note that a CT scan is not mandated as part of the study protocol but will be viewed prior to patient enrolment in cases where it was performed.
(5) Any other reason that the most responsible physician is uncomfortable enrolling the patient.

V. Study Procedures

A. Enrollment

Because most brain hypoxia occurs soon after ROSC, it is important that patients be enrolled as quickly as possible.

At Foothills Medical Center, cerebral oximetry can generally not be initiated until the patient is in an ICU. Thus, attempts should be made to transfer the patient out of the Emergency Department as rapidly as possible. Similarly, when patients undergo immediate cardiac catheterization, monitoring begins once the patient is admitted to CICU.

Given that the intervention arm of this study protocol is thought to pose minimal risk to patients and would, in fact, be considered “usual” care at some hospitals that routinely use cerebral oximetry (despite lack of proven efficacy), we will seek approval for deferred consent when alternate decisions makers are not immediately available. The next of kin should be approached as soon as feasible to provide informed consent.

B. Randomization

Randomization will be accomplished electronically using RedCap. The study team will be blinded to treatment allocation, which will be accomplished using variable blocks of 4 or 6, in a 1:1 ratio to intervention or control groups.

C. Initiation of Cerebral Oximetry

Cerebral oximetry pads will be placed bilaterally over the forehead. All patients will undergo insertion of an arterial catheter, as per usual practice. The cerebral oximetry machine (Root O_3, Masimo, Irvine, CA) and the bedside monitor (GE Carescape B650, GE Healthcare, Chicago, IL) will be attached to a laptop with ICM+ software (Cambridge, UK) using USB cables. Variables that will be recorded in ICM+ include blood pressure, ECG, arterial oxygen saturation, end-tidal CO_2 (available only in multi-system ICU), core body temperature (bladder) and rSO_2.

For patients that are allocated to the control group, a cover will be placed over the oximetry display and the rSO_2 values will not be shown in ICM+ or on the bedside monitor.

D. Study Groups

D1. Initial Goals

Initial physiologic goals will be consistent with International Liaison Committee on Resuscitation (ILCOR) guidelines, with MAP > 60-65 mmHg, PO2 75-100 mmHg, PCO2 35-45 mmHg, and temperature <37.5°C [30].

D2. Control Group

For patients randomized to the control group, these physiologic goals will continue unless otherwise indicated by the team responsible for care and clinicians will remain blinded to cerebral oximetry readings.

D3. Intervention Group

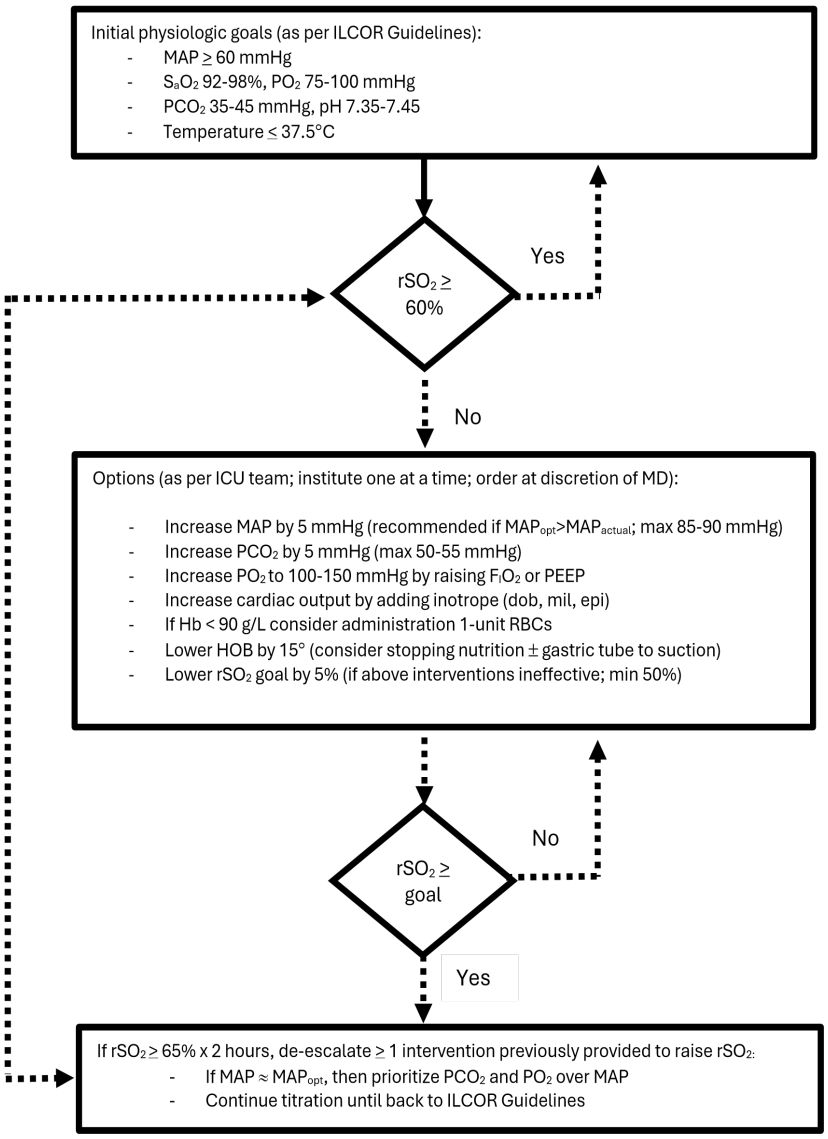
In the intervention group, cerebral oximetry will be utilized with the goal of keeping it at 60% or above.

If either rSO_2 value is less than 60% for more than 5 minutes, clinicians should intervene within 15 minutes. Treatment options will include (see also Figure):

- Raising MAP by about 5 mmHg at a time. This is the preferred option especially if actual MAP is below $MAP_{opt.}$ This can be achieved with either fluid administration or use of vasoactive drugs (inotrope or vasopressor). The maximum MAP target will be 85-90 mmHg.

- Augmenting cardiac output with either fluid administration, an inotrope (if left or right ventricular systolic function is impaired).

Figure. Management algorithm for COMPACT trial.



- Raising PO_2 to target 100-150 mmHg. This can be achieved with either higher F_IO_2, higher PEEP, or other interventions at the discretion of the clinical team (e.g., repositioning, inhaled vasodilator, pulmonary toilet, etc.). An arterial blood gas should generally be performed within 30-60 minutes to assess whether the PO_2 is in the goal range.
- Raising PCO_2 by about 5 mmHg. This can be achieved by reducing the minute ventilation (either respiratory rate or tidal volume). The maximum PCO_2 target will be 50-55 mmHg. In cases where, patients are spontaneously breathing and the PCO_2 is below the target range, clinicians may

choose to sedate the patient or administer a neuromuscular blocker. An arterial blood gas should generally be performed within 30-60 minutes to assess whether the PCO_2 is in the goal range.
- Lowering the head of bed by 15 degrees at a time. Consideration should be given to holding enteral nutrition and placing the nasogastric tube to suction.
- If the hemoglobin concentration is less than 90 g/L, transfusing 1 unit of red blood cells.

Which intervention to utilize, and the order of use, will be up to the most responsible clinician(s). If a particular intervention is considered unsafe, it does not need to be utilized. Interventions should generally be separated by at least 15 minutes, but moving on to another intervention (if rSO_2 is still below 60%) should not exceed 30 minutes.

If all interventions are ineffective at improving rSO2, it is reasonable to accept a lower the rSO2 target (reduce goal by 5% at a time, to a minimum 50%). If rSO2 is stable for 2-4 hours, previous interventions can be reversed in the order of least effect on rSO2. The protocol will be continued for 48 hours post arrest, following which management will be entirely as per the clinical team.

Once daily (in the morning of post-admission days 1 and 2), optimal MAP (MAP_{opt}) will be determined by the neurocritical care team. MAP_{opt} will be defined as the MAP where the cerebral oximetry index (COx) is lowest [31-32]. A graph relating COx (y-axis) with MAP range (in categories of 5 mmHg, e.g., 60.1-65, 65.1-70, 70.1-75, etc.) will be described as either U-shaped, ascending, descending, or indeterminate [33]. If the curve is U-shaped or descending, and the actual MAP target is below MAP_{opt}, the team caring for the patient will be notified and encouraged to consider raising the MAP target by about 5-10 mmHg (maximum 85-90 mmHg). If the clinical team does not consider the change in MAP to be safe, no change needs to be made. For example, if left ventricular function is severely impaired, and the most responsible clinician(s) do not believe the increased afterload incurred with a higher MAP target would be safe, no change will be made.

VI. Study Outcomes

A. Proof-of-Concept Outcomes

A1. Burden of Cerebral Hypoxia

The primary outcome will be "area under the curve" (AUC; time x severity) with critical rSO_2 levels below 60%. We hypothesize that the burden of cerebral hypoxia will be significantly lower in the study group compared with standard of care.

For each minute that the patient was monitored, the degree of reduction in rSO_2 will be summated. The sum per side will be divided by the number of minutes monitored to determine the average rSO_2 reduction. This will be multiplied by 2880 minutes (or 48 hours; the maximum number of minutes of monitoring) since some patients may have been monitored for less than a full 48 hours (e.g., if they died

or regained consciousness and were discharged from ICU). AUC will be summated between sides, since patients may have unilateral reductions in rSO_2.

AUC is expected to be lower in the intervention arm primarily among patients that have $rSO_2 < 60\%$ at the start of the recording. We are not certain what proportion of patients will have low rSO_2. Thus, our power calculation will be based on a reduction in AUC for all patients, but our main secondary outcome will be AUC specifically among patients with baseline $rSO_2 < 60\%$.

Additional outcomes will include:

- Percent time with $rSO_2 < 60\%$
- Percent time with $rSO_2 < 60\%$ in patients where initial $rSO_2 < 60\%$
- Change in rSO_2 over time in patients where initial $rSO_2 < 60\%$
- Percent time where MAP is > 5 mmHg higher or lower than MAP_{opt}

A2. Secondary Brain Injury (Serum Biomarkers)

Neuron specific enolase (NSE) is an intracellular glycolytic enzyme that is expressed primarily by neurons and becomes detectable in blood after neuronal injury. The magnitude of rise in NSE is strongly associated with a smaller chance of awakening from coma and has been recommended as a tool to use in assessment of neurologic prognosis, although there continues to be some debate regarding the specific threshold that should be used for this purpose [30].

Recent research has demonstrated that serum NSE levels are dynamic in the days following return of spontaneous circulation. Patients in whom NSE levels decline between 24 and 48-72-hours following resuscitation are more likely to have a favorable outcome compared with those in whom it continues to increase. NSE has a biological half-life of about 24 hours, such that an increment over time may reflect ongoing secondary neurologic injury. As such, the change over time is a potentially helpful endpoint to assess therapeutic interventions in the first few hours following ROSC [34]. For the purposes of this study, bedside clinicians will not be aware of NSE levels, which are not intended to be used in decision making regarding prognosis.

Neurofilament light is another biomarker arising from the neurovascular bundle. Elevated levels reflect axonal injury. NF-L was demonstrated in a systematic review to be the most accurate biomarker in predicting neurologic outcome [35]. Kinetics of NF-L may provide additional prognostic information [36].

Tau protein supports the cell structure and nutrient transport in neurons. It has a short half-life, and levels have been observed to increase in post-arrest patients between 24 and 72 hours, suggesting that it may be an indicator of secondary brain injury [35].

In a systematic review, NSE, NF-L, and tau protein were the three biomarkers with the greatest area under the curve in predicting outcomes post-arrest [35]. These biomarkers will be measured as soon as

possible upon admission to the ICU and on each morning (approximately 8 am) following admission for three consecutive days. Post-cardiac arrest patients almost invariably have an arterial or central venous catheter *in situ* such that no additional venipuncture will be required (arterial catheters will be prioritized for blood draws to standardize collection as much as possible). Because it is important to obtain baseline values as early as possible, initial samples will be drawn with a deferred consent model. Our analysis will determine whether the difference between baseline and day 3 biomarker levels is modified based on study group allocation.

B. Feasibility Outcomes

We hypothesize that enrolment will occur with a consent rate of at least 75% and at a rate of at least 2 patients per month. Determination of enrolment rate will assist in planning of future multi-center studies.

Adjustments of MAP, PO_2, PCO_2, are relatively simple interventions that are common in ICU practice. We therefore expect clinicians to be compliant. Protocol deviations will be recorded to understand potential barriers to future multi-center studies. Assessment of compliance will be particularly important in the CICU, where measures to augment CBF are not as commonly used as in the multi-system / neuro ICU.

C. Safety Outcomes

Serious adverse events (SAEs) will be recorded and compared between groups. These will include:

- Neurological: seizures, transtentorial herniation, and progression to death by neurological criteria.
- Cardiovascular: arrhythmias (ventricular tachycardia, atrial fibrillation, atrial flutter), recurrent cardiac arrest, and development of cardiogenic shock
- Respiratory: ARDS and cardiogenic pulmonary edema
- Gastrointestinal: mesenteric ischemia
- Renal: acute kidney injury (based on KDIGO definitions)

The neurocritical care team will assess optic nerve sheath diameter and pupillometry (NPi) once daily, as potential surrogates for intracranial pressure. These results will not be shared with clinians caring for the patient.

D. Patient-Centered Efficacy Outcomes

This study will be underpowered to assess the impact of a cerebral oximetry-guided protocol on neurological outcomes.

Nevertheless, we will record the following outcomes to obtain preliminary data and assess the association between neuromonitoring variables and outcome.

- Cerebral performance category score assessed at hospital discharge and 3 months and dichotomized into categories of favorable (1-2) and unfavorable (3-5) outcome.
- 28-day mortality

In hospital outcomes will be determined using the patient's medical record and direct assessment of the patient. 3-month outcomes will be obtained through the medical record and by telephone interviews whenever necessary. For the purposes of this study, it will not be possible to blind outcome adjudicators to treatment group.

VII. Clinical and Laboratory Evaluations

The following Table summarizes the schedule of events:

Event	Baseline (Day 0)	Day 1	Day 2	Day 3	Day 4 to ICU D/C	ICU D/C	3 months	Responsible
Screening	X							NCC RC
Randomization	X							RC
Record patient characteristics	X							RC
GCS score	X	X	X	X				NCC
PLR, corneal reflexes	X	X	X	X				NCC
Automated Pupillometry		X	X	X				NCC
Optic Nerve Sheath Diameter (average)	X	X	X	X				NCC
MAP_{opt} Determination		XX	XX					NCC
CPC Score						X	X	RC
Blood drawn for NSE, NF-L, & tau	X	X	X	X				NCC RC
Records results of any neuroimaging, EEG, SSEP	X	X	X	X	X			RC
Confirm ICM+ recording all data (including control patients)	X	X	X					NCC RC

VIII. Statistical Analysis Plan

With a sample size of 44 patients (22 per group), using alpha 0.05, we will have 90% power to detect an absolute difference of 10% in time spent with RSO_2 < 60% in the first 48 hours post-arrest (assuming a standard deviation of about 10%).

Numeric variables will be described using means with standard deviations or medians with interquartile ranges, depending on whether the data is normally distributed. Comparisons between study groups will be made using t-tests or Kruskall-Wallis tests for normally and skewed data, respectively. Categorical variables will be compared using chi-square analysis or Fisher's exact test (if any cell in a 2x2 table has a count of 5 of fewer).

Key numeric outcomes will include AUC (product of degree of rSO_2 reduction x time), percentage of monitoring time with rSO_2 < 60%, biomarker levels (difference between baseline and day 3 NSE, NF-L. and tau protein concentrations), pupillometry readings (NPi), and optic nerve sheath diameter. Key categorical outcomes will include dichotomized CPC scores (into categories of favorable and unfavorable), 28-day mortality, and serious adverse events.

Change in rSO_2 over time will be modeled using generalized estimating equation linear models with autoregressive correlation structure.

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