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Near-Infrared Spectroscopy to Assess Cerebral Autoregulation and Optimal Mean Arterial Pressure in Patients With Hypoxic-Ischemic Brain Injury: A Prospective Multicenter Feasibility Study

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Objectives: We provide preliminary multicenter data to suggest that recruitment and collection of physiologic data necessary to quantify cerebral autoregulation and individualized blood pressure targets are feasible in postcardiac arrest patients. We evaluated the feasibility of a multicenter protocol to enroll patients across centers, as well as collect continuous recording (≥ 80% of monitoring time) of regional cerebral oxygenation and mean arterial pressure, which is required to quantify cerebral autoregulation, using the cerebral oximetry index, and individualized optimal mean arterial pressure thresholds. Additionally, we conducted an exploratory analysis to assess if an increased percentage of monitoring time where mean arterial pressure was greater than or equal to 5 mm Hg below optimal mean arterial pressure, percentage of monitoring time with dysfunctional cerebral autoregulation (i.e., cerebral oximetry index ≥ 0.3), and time to return of spontaneous circulation were associated with an unfavorable neurologic outcome (i.e., 6-mo Cerebral Performance Category score ≥ 3).

Design, Setting, and Patients: A prospective multicenter cohort study was conducted in ICUs in three teaching hospitals across Canada. Patients (≥ 16 yr old) were included if their cardiac arrest occurred within the previous 36 hours, they had greater than or equal to 20 consecutive minutes of spontaneous circulation following resuscitation, and they had a post-resuscitation Glasgow Coma Scale of less than or equal to 8.

Measurements and Main Results: Recruitment rates were calculated across sites, and patients underwent continuous regional cerebral oxygenation monitoring using near-infrared spectroscopy, as well as

invasive blood pressure monitoring. Exploratory multivariable logistic regression was performed. Although it was feasible to recruit patients across multiple centers, there was variability in the recruitment rates. Physiologic data were captured in 86.2% of the total monitoring time and the median monitoring time was 47.5 hours (interquartile interval, 29.4–65.0 hr) across 59 patients. Specifically, 88% of mean arterial pressure and 96% of bilateral frontal regional cerebral oxygenation data were acquired, and 90% of cerebral oximetry index and 70% of optimal mean arterial pressure values were quantified. However, there was substantial variation in the amount of data captured among individuals. Time to return of spontaneous circulation was associated with an increased odds of an unfavorable neurologic outcome.

Conclusions and Relevance: We demonstrated feasibility to recruit and collect high frequency physiologic data in patients after cardiac arrest. Future investigations will need to systematically document the reasons for data attrition, as well as how these methodological complications were resolved. Due to underpowered analyses and the inability to control for potential confounds, further studies are needed to explore the association between cerebral autoregulatory capacity and individualized mean arterial pressure thresholds with neurologic outcomes.

Key Words: cardiac arrest; cerebral autoregulation; hypoxic-ischemic brain injury; near-infrared spectroscopy; optimal mean arterial pressure

Cardiac arrest is a devastating event that frequently results in hypoxic-ischemic brain injury (HIBI) from inadequate or absent cerebral blood flow (CBF). Among survivors, the vast majority of subsequent deaths are directly attributable to HIBI, and less than 50% of survivors have a favorable neurologic outcome, assessed using the Cerebral Performance Category (CPC), 6 months post-arrest (1). HIBI is characterized by multiple mechanisms that occur in parallel, such as failure of microcirculation, no-reflow cerebral edema, tissue hypoxia (2), elevated intracranial pressure, and dysfunctional cerebral autoregulation (3, 4). As such, maintaining adequate CBF and cerebral oxygen delivery is paramount in post-resuscitation care (5). However, studies in patients following cardiac arrest demonstrate that the autoregulatory plateau is narrowed and right-shifted, with marked between-patient heterogeneity (4, 6, 7). Notwithstanding, the American Heart Association guidelines recommend maintaining mean arterial pressure (MAP) greater than 65 mm Hg in all patients post-arrest (8).

Near-infrared spectroscopy (NIRS) is a noninvasive measure of regional cerebral oxygenation (rSo_2). A sensor and light source, which emit and receive varying wavelengths of near-infrared light (700–1,000 nm), are placed on the forehead (9). Based on the attenuation and scattering of light, rSo_2 is calculated and indicates the proportion of oxygenated to deoxygenated hemoglobin concentration (10). Cerebral autoregulation can be calculated by computing the time-varying association between MAP and rSo_2, termed the cerebral oximetry index (COx) (11). COx has been previously been validated as a bedside measure of cerebral autoregulation in multiple populations, including those with: stroke (12), sepsis (11), and subarachnoid hemorrhage (13). In addition, COx can be used to identify individualized zones of optimal MAP (MAP_{OPT}), which are characterized by intact autoregulation (i.e., rSo_2 remains stable despite changes in MAP).

Our previous single-center proof-of-concept study demonstrated that it was also feasible to generate both COx and MAP_{OPT} in 20 patients following cardiac arrest (6). However, it was unclear if we could obtain sufficient patient recruitment, data acquisition, and characterization of neurologic outcomes at other sites. Therefore, the primary objective of this multicenter study was to determine 1) the feasibility of recruitment rates across sites to guide a larger cohort study and 2) the feasibility of continuous concurrent monitoring of rSo_2 and MAP in postcardiac arrest patients. We additionally aimed to test exploratory hypotheses that increased percentage of monitoring time where the actual MAP with greater than or equal to 5 mm Hg below from individual MAP_{OPT}, percentage of monitoring time with dysfunctional cerebral autoregulation (i.e., COx ≥ 0.3), and time (i.e., min) to return of spontaneous circulation (ROSC) were associated with an increased likelihood of an unfavorable neurologic outcome post-arrest.

MATERIALS AND METHODS

Study Design and Participant Recruitment

The Cerebral Oximetry to Assess Cerebral Autoregulation in Hypoxic-Ischemic Brain Injury study was a prospective multicenter feasibility study across three Canadian sites: Vancouver General Hospital (Vancouver, BC, Canada), St. Paul's Hospital (Vancouver, BC, Canada), and Sunnybrook Health Sciences Center (Toronto, ON, Canada). The local Research Ethics Board at each site approved the protocol and patients were approached by research staff to obtain informed consent. If the patient was unable to provide consent, the legal authorized representative (LAR) was contacted. When a LAR was not available, a deferred consent model was implemented until informed consent could be obtained from the LAR or if the patient regained capacity. Patients (≥ 16 yr old) admitted to the ICU or coronary care unit were eligible for enrollment if their arrest occurred within the previous 36 hours, they had greater than or equal to 20 consecutive minutes of spontaneous circulation following resuscitation, and had a post-resuscitation Glasgow Coma Scale (GCS) of less than or equal to 8. Patients were excluded if there were no plans for ongoing supportive care, if there was a history of cardiac arrest (i.e., previous arrest indicated on medical records), traumatic brain injury (TBI), intracranial hemorrhage, or ischemic stroke, in order to minimize the confounding that other structural disease processes may potentially have on the rSo_2 signal and cerebral autoregulation assessment. All post-resuscitation treatments were left to the discretion of the attending physician, which included the institution and management of targeted temperature management.

Demographics and Clinical Characteristics

Basic clinical characteristics and demographic information (e.g., age, sex, admission GCS, etiology for cardiac arrest, and comorbidities) were collected at the time of study enrollment. These data were entered by each site into the Research Electronic Data Capture online application.

Multimodal Monitoring and Quantification of Cerebral Autoregulation and MAP_{OPT}

Continuous rSo_2 monitoring was implemented for ~72 hours using the INVOS oximeter (Medtronic, Dublin, Ireland). Two sensors were placed bilaterally in the frontotemporal position. rSo_2 and arterial line data (i.e., MAP) were both resampled to 10-second intervals using ICM+ brain monitoring software (Cambridge Enterprise, Cambridge, United Kingdom). COx was calculated by ICM+ as a moving Pearson correlation coefficient (a value ranging from –1 and +1) between 30-consecutive, 10-second averaged values of MAP and corresponding rSo_2 signals. A positive COx value of greater than or equal to 0.3 was considered to indicate dysfunctional autoregulation (14). MAP_{OPT} was calculated using a multi-window weighted algorithm (ICM+ "OptimalValueFlex" function) (15). This algorithm generates a U-shaped curve plotted through the COx values across 5 mm Hg bins of MAP per patient. Compared to a 4-hour moving window (16), the multi-window weighting approach uses data from 36 windows of between 2 and 8 hours in duration. The summative MAP_{OPT} is generated whereby curves with a better U-shape (compared with accelerating or decelerating forms) and those with a more negative nadir COx are given more weight. This approach increases the yield and stability of determining MAP_{OPT} compared to a time-window with a constant size. We subsequently calculated the difference between the actual MAP and MAP_{OPT} (ΔMAP). Furthermore, medical staff were not blinded to the rSo_2 recordings as these values are not routinely used to guide care across institutions. As this was not an interventional trial, clinicians were blinded to the COx and MAP_{OPT} recordings to reduce potential treatment bias as these variables are frequently used in interventional trials. Finally, we averaged all of the physiologic data over 10-minute epochs.

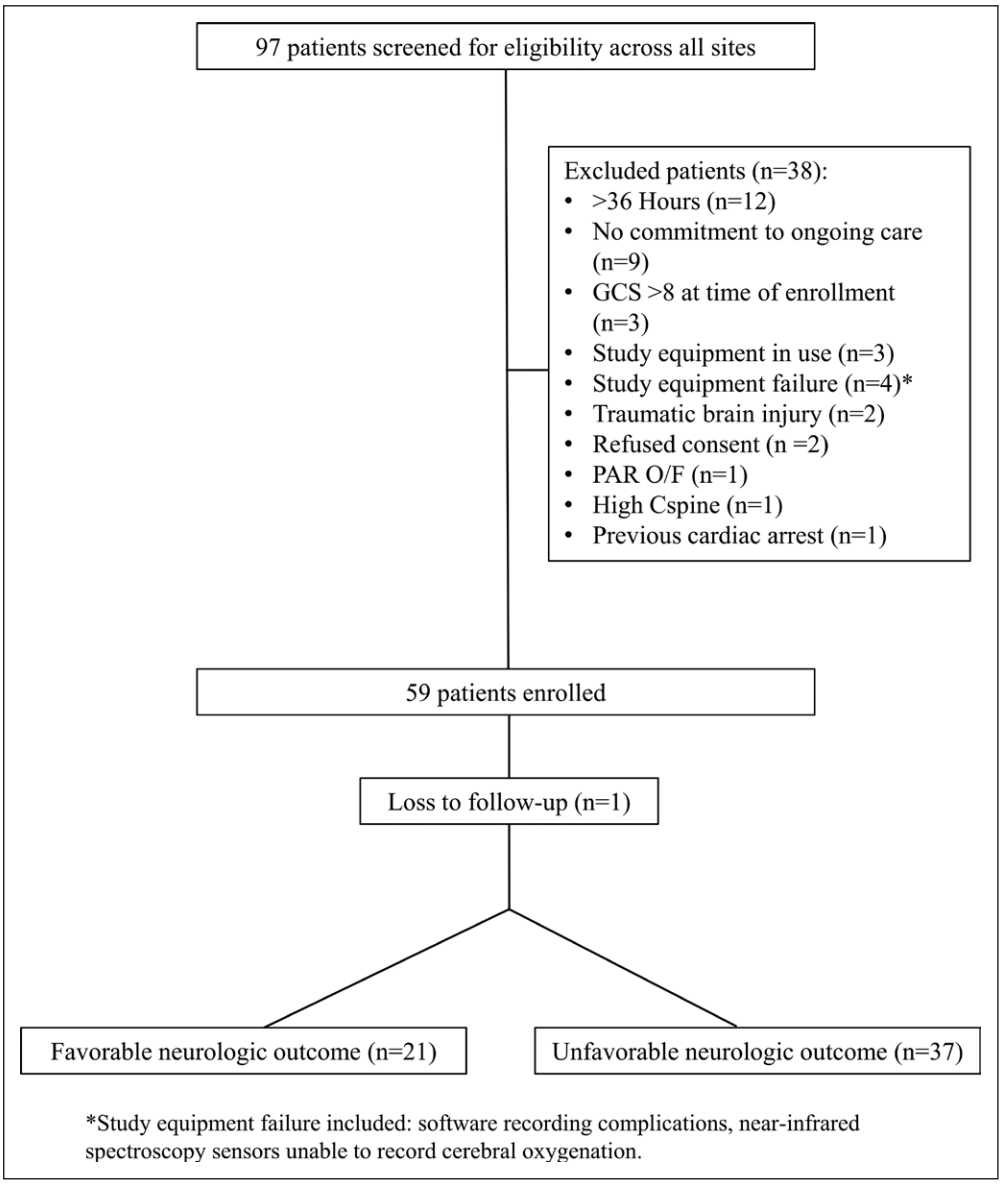

Figure 1. Consolidated Standards of Reporting Trials diagram indicating patient screening and subsequent inclusion and exclusion during patient recruitment. Cspine = cervical spine injury, GCS = Glasgow Coma Scale, PAR O/F = post-anesthetic recovery over-flow.

Outcome Measures: Neurologic Disability and Mortality

The CPC is scored on a 5-point scale: 1 (good cerebral performance—normal life), 2 (moderate cerebral disability—disabled but independent), 3 (severe cerebral disability—conscious but disabled and dependent), 4 (coma/vegetative state—unconscious), and 5 (brain death). The CPC was administered by trained research staff, who were blinded to the physiologic data collected in the ICU, to either the patient or their LAR over the telephone at 6 months after ICU discharge. Medical records were consulted to verify CPC scores greater than or equal to 4. Participants with a CPC of greater than or equal to 3 were classified as having an unfavorable outcome.

Data Cleaning: Detecting and Editing Anomalies

High frequency vital sign recordings have been previously shown to contain a substantial burden of artifact (17). We used custom algorithms to implement data cleaning procedures to minimize the inclusion of these anomalous data. Specifically, MAP and MAP_{OPT} less than 40 mm Hg and greater than 140 mm Hg and rSo_2 less than 20 were treated as missing data, as these values were deemed anomalous. To further quantify data quality and completeness, we stratified patients based on patterns of missingness.

Data Analysis: Sample Size, Primary, and Secondary Outcomes

An a priori power or sample size calculation was not conducted. The sample size was one of convenience and represents the largest cohort that could be achieved within study resources. Based on five patients recruited per month in our pilot study, one to two patients per month per center would be required to demonstrate multicenter feasibility (6). Thus, we defined feasibility a priori as the ability to enroll 1.5 patients (i.e., between one and two patients) per month. Additional feasibility metrics were as follows: 1) Ability to collect greater than or equal to 80% of rSo_2 (both right and left sensors) and MAP data into ICM+ for the total monitoring time across all patients. These two physiologic metrics are necessary to calculate COx and MAP_{OPT} and are therefore imperative to assess feasibility of continuous neuromonitoring. 2) Ability to collect 6-month CPC scores for all participants.

Logistic Regression

Multivariable logistic regression was used to assess potential predictors of an unfavorable neurologic outcome. We selected the following independent variables a priori as they were likely to be associated with HIBI post-arrest and subsequent neurologic dysfunction: 1) the percentage of time where the ΔMAP was less than 5 mm Hg (6), 2) percentage of time with dysfunctional cerebral autoregulation (i.e., COx ≥ 0.3) (12, 14), and 3) time in minutes to ROSC. All statistical analyses were performed using R software Version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) (18). The logistic

TABLE 1. Demographics and Clinical Characteristics

Variables	Total, *n* = 59	Favorable Outcome (CPC 1 and 2), *n* = 21	Unfavorable Outcome (CPC 3–5), *n* = 37
Age, yr	58.0 (42.5–66.0)	53.0 (38.0–60.0)	59.5 (48.0–67.0)
Female sex	13 (22%)	5 (24%)	8 (21%)
Acute Physiology and Chronic Health Evaluation II score	26.0 (20.0–35.0)	25.0 (20.0–35.0)	26.5 (20.0–35.0)
Glasgow Coma Scale motor score			
1	41 (68%)	13 (62%)	28 (74%)
2	4 (7%)	1 (5%)	3 (8%)
3	7 (12%)	2 (10%)	4 (11%)
4	8 (13%)	5 (24%)	3 (8%)
Out-of-hospital cardiac arrest	32 (53%)	10 (48%)	22 (58%)
Initial rhythm			
Asystole	13 (22%)	2 (10%)	11 (29%)
Pulseless electrical activity	33 (56%)	9 (45%)	23 (61%)
Ventricular fibrillation/ventricular tachycardia	13 (22%)	9 (45%)	4 (11%)
Etiology of arrest			
Hypovolemia	7 (12%)	2 (10%)	5 (13%)
Hypoxemia	20 (33%)	3 (14%)	16 (42%)
Myocardial infarction	10 (17%)	4 (19%)	6 (16%)
Other	21 (35%)	10 (48%)	11 (29%)
Pulmonary embolism	2 (3%)	2 (10%)	0 (0%)
Minutes prior to return of spontaneous circulation	17.5 (10.5–30.0)	11.0 (5.0–21.0)	21.0 (13.0–31.0)
Hypertension	22 (37%)	6 (29%)	16 (42%)
Current smoker	17 (28%)	4 (19%)	12 (32%)
Coronary artery disease	9 (15%)	1 (5%)	7 (18%)
Type II diabetes mellitus	7 (12%)	2 (10%)	5 (13%)
Dyslipidemia	13 (22%)	2 (10%)	10 (26%)

CPC = Cerebral Performance Category.
Data are presented as median (interquartile interval) for continuous measures, and *n* (%) for categorical measures.

regression model and independent variables were considered statistically significant if *p* value of less than 0.05.

RESULTS

Recruitment, Demographic, and Clinical Characteristics

From June 2016 to December 2017, 97 patients were screened for eligibility. Thirty-eight patients were excluded for meeting at least one exclusion criteria (**Fig. 1**), four were not included in the final analysis due to equipment failure, resulting in 59 patients (1.5 patients per site per month) being enrolled. The total number of months of screening per site (site A = 17.5, site B =10, site C =8), average number of patients recruited per month (site A = 2.0, site B = 2.0, site C = 0.5), and total number of patients recruited (site A = 35, site B = 20, site C = 4) were variable across sites. Baseline characteristics are summarized in **Table 1**. Briefly, the total cohort had a median age of 58 years (interquartile interval [IQI], 42.5–66.0 yr) and was mostly male (46/59, 78%). At admission, the median Acute Physiology and Chronic Health Evaluation II score was 26 (IQI, 20–35) and most presented with a GCS motor score of 1 (41/59, 68%). The three most common comorbidities were hypertension (22/59, 37%), current smoker (17/59, 28%), and dyslipidemia (13/59, 22%). The median time to ROSC was 17.5 minutes (IQI, 10.5–30.0 min) and 32 of 59 patients (53%) had an out-of-hospital cardiac arrest. Overall, 36 of 59 patients (61%) died either in hospital or by 6 months.

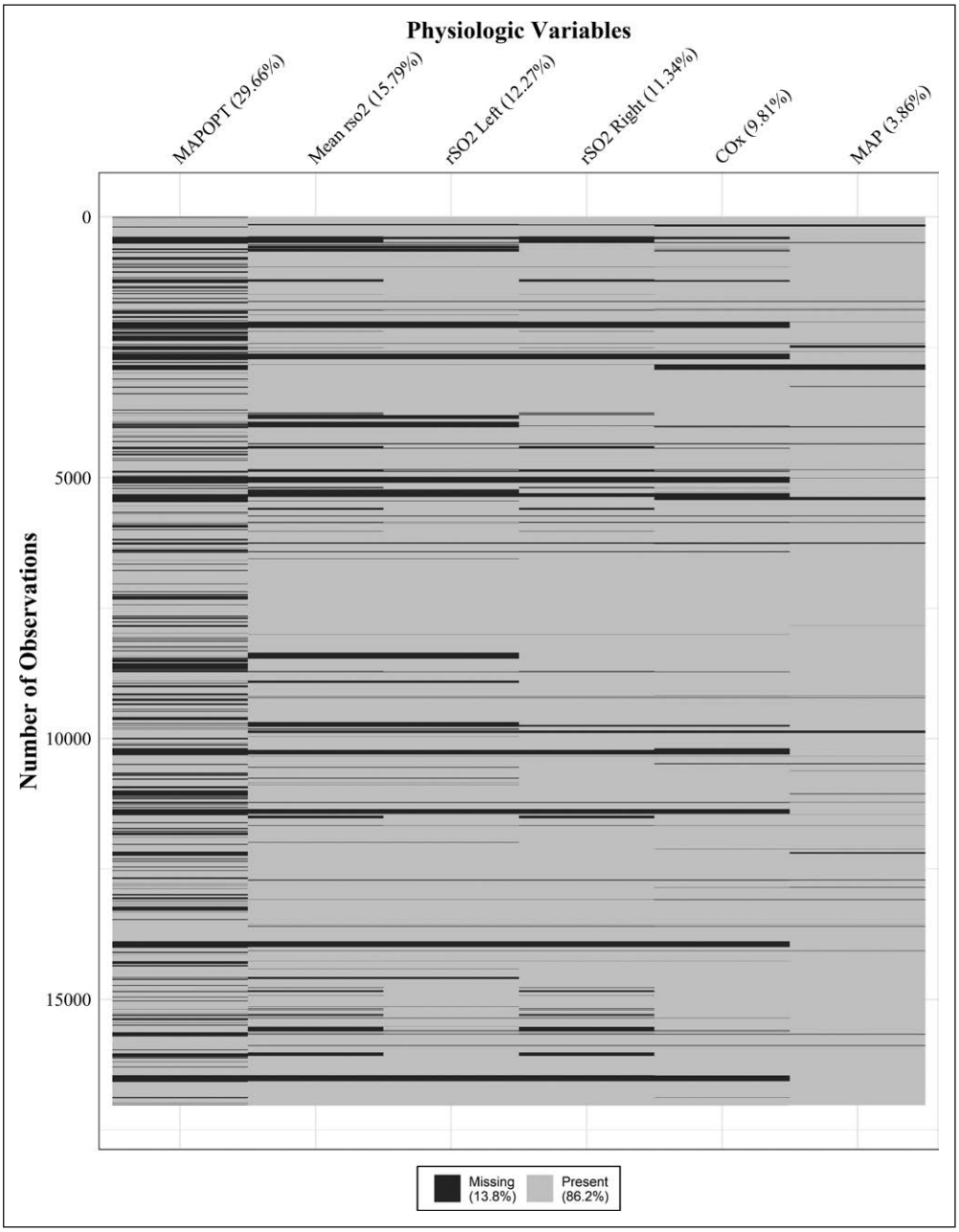

Figure 2. A heatmap to visually represent the total number of data points collapsed across all patients (i.e., 17,028) shown in *rows*, with each *column* representing a physiologic variable (e.g., mean arterial pressure [MAP]) recorded throughout the monitoring period. *Black shading* represents missing or anomalous data, whereas *gray shading* represents present recordings. Increasing *line thickness* represents sequential data points that data were successfully recorded (*gray*) or missing/anomalous (*black*). The order on the *y*-axis simply represents the observation number. COx = cerebral oximetry index, MAP_{OPT} = optimal mean arterial pressure, rSo_2 = regional cerebral oxygenation.

Physiologic Data Capture and Outcome Assessments

Monitoring time demonstrated high variability with a median of 47.5 hours (IQI, 29.4–65.0 hr). Across all patients, averaged 10-minute segments of physiologic variable acquisition were as follows: MAP 16,370 of 17,028 (96%), left rSo_2 sensor 14,938 of 17,028 (88%), and right rSo_2 sensor 15,097 of 17,028 (89%). ICM+ was able to quantify COx in 15,358 of 17,028 (90%), and MAP_{OPT} in 11,978 of 17,028 (70%). Overall, 86.2% of the available data were captured and 13.8% were deemed missing or anomalous (**Fig. 2**). However, substantial variability was observed in the amount of data that were successfully captured across physiologic metrics and among individuals (**Table 2** and **Fig. 3**). Furthermore, we identified three patterns of missingness. Pattern 1, 20 of 59 patients (34%) had successful data collection (≥ 80%) across all physiologic variables (i.e., MAP, left rSo_2, right rSo_2, mean rSo_2, COx, and MAP_{OPT}). Pattern 2, 23 of 59 (39%) had successful data collection across all variables but unsuccessfully quantified (< 80%) MAP_{OPT},

TABLE 2. Amount of Data Successfully Captured (≥ 80%) Across Cardiac Arrest Patients

Physiologic Variables	Median Amount of Data Successfully Captured (IQR)	No. of Patients With Successful Data Capture (%)
Mean arterial pressure	99.7% (95.3–100%)	57/59 (97)
rSo_2 left	96.6% (86.2–99.8%)	47/59 (80%)
rSo_2 right	96.9% (83.5–100%)	48/59 (81%)
rSo_2 across sensors	95.0% (80.0–99.6%)	44/59 (75%)
Cerebral oximetry index	96.8% (87.7–100%)	48/59 (81%)
Optimal mean arterial pressure	70.9% (59.5–84.4%)	19/59 (32%)

IQR = interquartile range, rSo_2 = regional cerebral oxygenation.

which may indicate software failure. Pattern 3, 16 of 59 (27%) had unsuccessful data collection (< 80%) of rSo_2 or MAP (i.e., potential equipment failure) and could not subsequently quantify secondary and tertiary variables. Despite this missingness variability, these three patterns were comprised of patients with similar demographics and clinical characteristics (**Table 3**). At 6 months, CPC scores were obtained for 58 of 59 patients (98%), and thus, one patient was not included in outcome analysis. The distribution of CPC scores were as follows: 1 (n = 19), 2 (n = 2), 3 (n = 1), and 5 (n = 36).

Six-Month Neurologic Outcomes: Demographics, Clinical Characteristics, and Neuromonitoring

Clinical and physiologic characteristics stratified by neurologic outcome are presented in Table 1. Compared to patients with a 6-month favorable neurologic outcome, we observed that those with unfavorable outcomes had a higher proportion of cardiac arrest associated with hypoxemia, presence of chronic comorbidities (e.g., hypertension, diabetes, and coronary artery disease), out-of-hospital arrest, and a longer median duration until ROSC. Neurophysiologic variables were similar in those with favorable and unfavorable outcomes (**Supplementary Table 1**, http://links.lww.com/CCX/A342 and **Supplementary Fig. 1**, http://links.lww.com/CCX/A356), as was the percentage of time with ΔMAP below –5 mm Hg and percent of time with dysfunctional cerebral autoregulation (COx ≥ 0.3).

Exploratory Outcome Analysis

A multivariable logistic regression model was fit to ascertain the effects that the percentage of time with ΔMAP below –5 mm Hg, the percentage of time with dysfunctional autoregulation (i.e., COx ≥ 0.3), and duration until ROSC have on the likelihood that postcardiac arrest patients have an unfavorable outcome. The multivariate model was statistically significant, p = 0.04, and accounted for approximately 19% of the observed variance (Nagelkerke pseudo R^2). Additionally, the logistic regression analysis demonstrated that each 1-minute increase in the time until ROSC after arrest significantly increased the odds of having an unfavorable neurologic outcome (odds ratio, 1.06/min; 95% CI, 1.02–1.12; p = 0.02; **Supplementary Table 2**, http://links.lww.com/CCX/A343). In a sensitivity analysis, age (as a continuous linear variable) and sex were included as covariates. However, including these covariates did not substantially alter the results (data not shown).

DISCUSSION

In this prospective multicenter study, we showed that it was feasible to recruit patients after cardiac arrest (> 1.5 patient per month) and to achieve comprehensive rSo_2 and MAP data collection in the majority of cases (≥ 80% of total monitoring time). Although other studies have similarly demonstrated feasibility to collect these primary data (19–21), we additionally were able to determine COx and MAP_{OPT} in 90% and 70%, respectively. However, quantification of these secondary and tertiary derived variables was exploratory and varied considerably across participants. Although we were able to ascertain CPC scores in 98% of patients, we did not achieve our feasibility goal of 100%. However, it may have been an unrealistic to achieve 100% data collection. Furthermore, there was variability in the recruitment rate across sites. In addition, a small number of participants (n = 4) were excluded due to equipment failure and there was substantial variation in the amount of successfully captured data among included participants. Future investigations will need to systematically document the reasons for data attrition (e.g., patient disconnect due to transfer for a procedure, software crash, and NIRS monitor not recording), as well as how these complications were resolved (e.g., plug-in monitor once in procedure room, update software, replace cerebral oximeter sensor). Furthermore, there were no substantial differences in blood pressure, cerebral oxygenation, or cerebral autoregulation metrics observed between groups. In contrast, increased time to ROSC was identified as a predictor of an unfavorable neurologic outcome in our exploratory analysis that will need to be validated in a new cohort of patients.

Post hoc inspection of the data revealed substantial variability in the amount of data that were successfully captured across physiologic metrics and among individuals. Pattern 1 of missingness indicated the ideal cohort of patients in which the majority of all physiologic data were captured, as well as the successful quantification of secondary and tertiary derived variables (i.e., COx and MAP_{OPT}). Pattern 2 indicated that rSo_2 and MAP were successfully captured for the majority of the monitoring period, as well as COx. However, MAP_{OPT} could not be successfully quantified, which likely indicates software failure. Unfortunately, the technological

reason for this complication could not be specifically identified nor resolved, which may hinder future multicenter analyses. Pattern 3 indicated that MAP was successfully recorded in most participants, but rSo_2 was not successfully captured, and thus, COx and MAP_{OPT} could not be quantified. Although the reasons for this lack of rSo_2 being captured were not documented, this finding highlights that future trials will need to systematically monitor data attrition and provide further neuromonitoring support at bedside (e.g., routine inspection of the rSo_2 monitor to ensure successful recording, replace or provide additional adhesive to ensure good skin contact with sensors). Fortunately, we were able to successfully collect the primary variables (i.e., MAP and rSo_2) in the majority of patients. The secondary (COx) and tertiary (MAP_{OPT}) derived variables were calculated for 90% and 70% of total monitoring time, respectively. Importantly, continuous data are subject to noise and artifact and including these missing and spurious data results in bias (22). Missing data can either be ignored, potentially introducing bias, or methods can be used to impute values (e.g., multiple imputation) if data can be assumed to be missing at random (23, 24). In order to reduce potential bias, we removed data that was deemed anomalous, did not impute missing values, and reduced to metrics to median values for analysis.

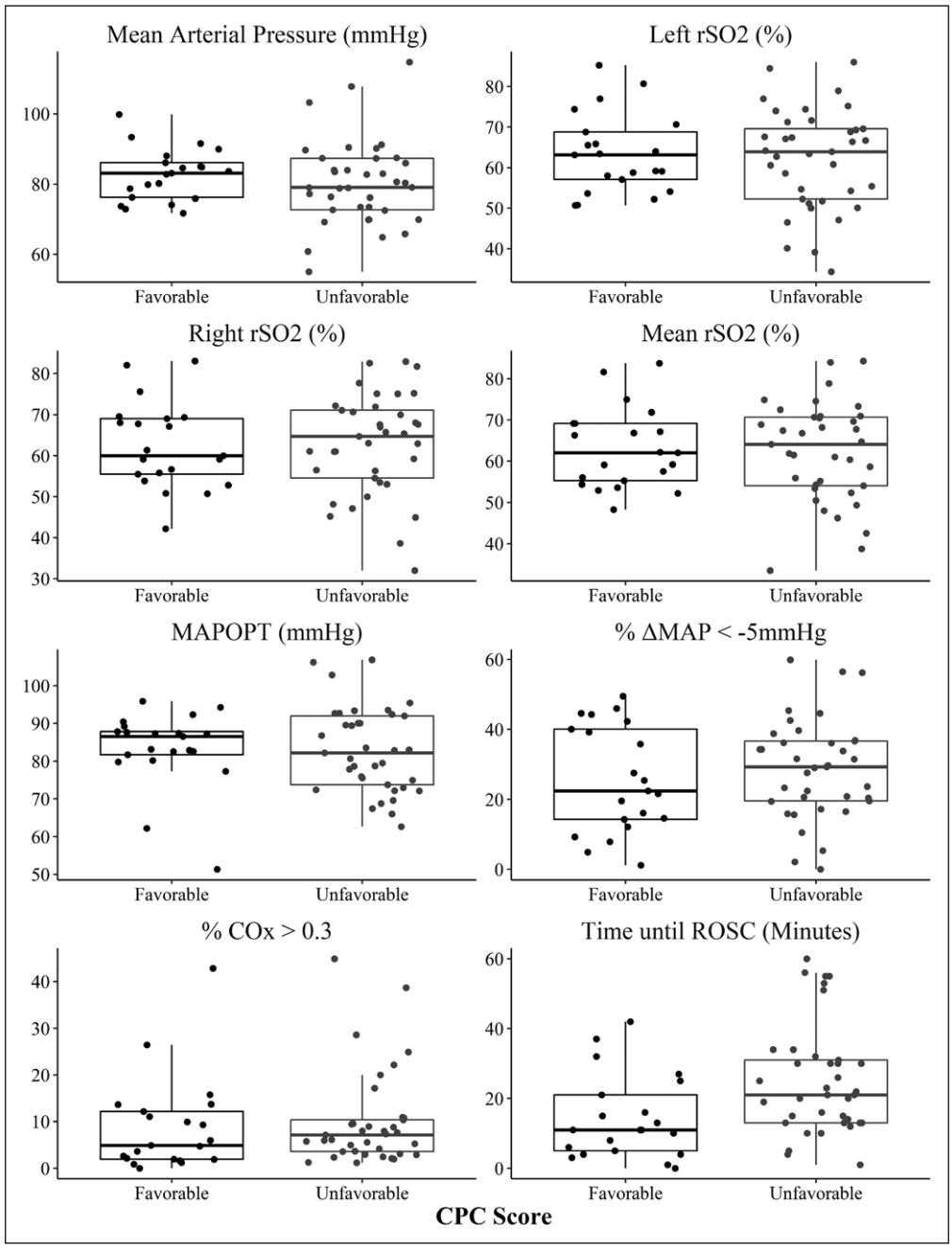

Figure 3. *Lollipop plots* indicating a high amount of individual variability in the percentage of data missing across physiologic variables. COx = cerebral oximetry index, CPC = Cerebral Performance Category, MAP_{OPT} = optimal mean arterial pressure, ROSC = return of spontaneous circulation, rSo_2 = regional cerebral oxygenation, ΔMAP = difference between mean arterial pressure and optimal mean arterial pressure.

Previous studies examining tertiary derived variables of neurophysiologic data (e.g., optimal cerebral perfusion pressure) were able to quantify these metrics in approximately half of the recording period (16, 25). Using a multi-window weighted algorithm (15), we obtained MAP_{OPT} in approximately 70% of total monitoring, despite a small amount of missing primary data. This may reflect methodological differences, using rSo_2 rather than intracranial pressure, which has been used as the correlational variable for MAP in the previously mentioned studies.

Observational studies (26–28) and a systematic review (29) have suggested that higher MAP values are associated with improved neurologic outcomes in patients with cardiac arrest. However, this association is not uniform. For example, a randomized controlled trial examining an early goal-directed hemodynamic strategy (MAP 85–100 mm Hg and mixed venous oxygen saturation 65–75%) resulted in improved rSo_2 compared with a MAP greater than 65 mm Hg strategy (30). Importantly, this improvement in rSo_2 did not translate to improved imaging correlates or neurologic outcomes (30). Our group has recently performed a prospective interventional study of invasive neuromonitoring in patients who remained comatose after cardiac arrest (2). This study demonstrated that the percentage of time with brain tissue hypoxia (partial pressure of brain tissue oxygen

TABLE 3. Patterns of Data Missingness Among Cardiac Arrest Patients

Variables	Pattern 1, *n* = 20	Pattern 2, *n* = 23	Pattern 3, *n* = 16
Age, yr	59 (50–73)	58.0 (47–65)	54 (38.75–67.5)
Female sex	5 (25%)	5 (21.7%)	3 (18.8%)
Acute Physiology and Chronic Health Evaluation II score	26 (19.75–35.25)	31 (23.5–35.0)	23 (14.75–27)
Glasgow Coma Scale motor score			
1	16 (80%)	16 (69.6%)	8 (50%)
2	1 (5%)	1 (4.3%)	2 (12.5%)
3	1 (5%)	5 (21.7%)	1 (6.3%)
4	2 (10%)	1 (4.3%)	5 (31.3%)
Initial rhythm			
Asystole	4 (20%)	5 (21.7%)	3 (18.8%)
Pulseless electrical activity	13 (65%)	14 (60.9%)	7 (43.8%)
Ventricular fibrillation/Ventricular tachycardia	3 (15%)	4 (17.4%)	6 (37.5%)
Etiology of arrest			
Hypovolemia	5 (25%)	2 (8.7%)	0 (%)
Hypoxemia	5 (25%)	7 (30.4%)	7 (43.8%)
Myocardial infarction	3 (15%)	4 (17.4%)	3 (18.8%)
Other	7 (35%)	8 (34.8%)	6 (37.5%)
Pulmonary embolism	0	2 (8.7%)	0
Minutes prior to return of spontaneous circulation	18.5 (10–27)	20 (14.5–34.0)	13 (9–30)
Hypertension	8 (40%)	7 (30.4%)	7 (43.8%)
Current smoker	3 (15%)	7 (30.4%)	7 (43.8%)
Coronary artery disease	2 (10%)	5 (21.7%)	2 (12.5%)
Type II diabetes mellitus	3 (15%)	3 (13%)	1 (6.3%)
Dyslipidemia	5 (25%)	5 (21.7%)	3 (18.8%)
Hours monitored	36 (26.54–68.88)	50 (30.75–68.17)	47.5 (33.25–53.04)
Percentage of recording:			
Mean arterial pressure	100 (96–100)	100 (95–100)	96.5 (93.75–100)
Cerebral oximetry index	99 (96.75–100)	99 (95–100)	73 (51.75–83.5)
Optimal mean arterial pressure	88.5 (84.5–92.25)	64 (52.5–69.5)	63.5 (41.75–71)
Mean rSo_2	97 (94–100)	98 (89.5–100)	43 (35.5–66.25)
rSo_2 left	98 (96.75–100)	99 (94.5–100)	54.5 (41.25–79.75)
rSo_2 right	99.5 (95.75–100)	99 (94–100)	70 (41.25–85.25)
Mortality	13 (65%)	16 (69.6%)	7 (43.8%)

rSo_2 = regional cerebral oxygenation.

Data are presented as median (interquartile range) for continuous measures, and *n* (%) for categorical measures.

Pattern 1 represents ≥ 80% of successful recordings across all variables. Pattern 2 represents < 80% of optimal mean arterial pressure (MAP_{OPT}) recordings, but ≥ 80% of successful recordings across all other variables. Pattern 3 represents < 80% MAP_{OPT} recordings, and at least one other variable with < 80%. This group was composed of patients missing rSo_2 data, except for one patient who had < 80% of mean arterial pressure recordings.

[$Pbto_2$] < 20 mm Hg) was common, despite average MAP_{OPT} recordings being 89 mm Hg (2). Notably, when MAP approached MAP_{OPT}, there was a substantial improvement in $PbtO_2$, suggesting that the individualized MAP may be important in increasing oxygen in brain tissue rather than generalized MAP targets (i.e., ≥ 65 mm Hg).

Other studies have examined the use of NIRS in patients following cardiac arrest. Ameloot et al (7) demonstrated that 33

of 51 patients (65%) had "preserved" autoregulation, which was associated with improved survival at 180 days. In patients where a MAP_{OPT} could be calculated, the time under this threshold was negatively associated with survival (7). In contrast, time under fixed thresholds (≥ 65 mm Hg) was not associated with survival. Pham et al (31) also examined cerebral autoregulation using NIRS in patients after cardiac arrest. Improved cerebral autoregulation was associated with survival, whereas there was no significant association observed with the raw cerebral oxygenation values (31). We did not observe any substantial differences in rSo_2, ΔMAP, MAP_{OPT}, or COx values between patients with unfavorable and favorable neurologic outcomes. However, our analysis was purely exploratory and was likely underpowered due to a small sample size, as well as unable to adjust for potential confounders (e.g., medication dosing, body temperature). Therefore, further work is needed to build more comprehensive models to assess neurophysiologic variables associated with outcome postcardiac arrest.

Despite being a multicenter trial, the majority of participants were recruited at the coordinating center, which may limit external generalizability. Another limitation, common to all nonrandomized trials, is that unmeasured or residual confounding could be an alternate explanation for our findings. For example, it remains unclear if high NIRS recordings indicate the inability to extract adequate oxygen due to the primary injury regardless of MAP changes or if high rSo_2 values indicate increased oxygen delivery to tissue. Furthermore, we had to exclude four participants due to equipment failure (i.e., their data could not be collected), which may have slightly biased our findings. Although rSo_2 monitoring was aimed at ~72 hours, variability in monitoring lengths was observed as NIRS recording frequently ceased at a time that was convenient for the patient (e.g., regained mental capacity), the medical team (e.g., transfers for various procedures), or research staff. However, this was not systematically documented. Future trials will need to ensure that patients are monitored for comparable recording lengths as cerebral autoregulatory capacity may change over time. A larger cohort of postcardiac arrest patients will be needed to statistically model covariates and confounds that have been shown to associated with the NIRS-derived rSo_2 signal (e.g., Pco_2, heart rate, hemoglobin concentration, arterial oxygen saturation, body temperature) and thus cerebral autoregulation (32–34). As arrest etiology has been previously implicated as an important source of between-patient heterogeneity in regard to neurologic and cardiovascular injury (35), future investigations will require either a homogenous arrest cohort (e.g., myocardial infarction) or a representative sample size powered to conduct subgroup statistical analyses. The impact of missing and spurious data on COx and MAP_{OPT} (e.g., multiple imputation contrasted with comparator data with missingness) will also need to be assessed. Comparing different lengths of the multi-window weighted algorithm (e.g., 2 vs 4 vs 8 hr) and the impact on MAP_{OPT} would also be of interest, as this technique has been previously explored in patients with TBI (15) and delirium (36). Additionally, there may be other methods (e.g., differential entropy) to examine for higher-order relationships and improve the assessment of MAP_{OPT} (37).

CONCLUSIONS

We demonstrated that it was feasible to recruit patients and continuously collect high frequency noninvasive physiologic data in patients after cardiac arrest. Time below MAP_{OPT} and duration of dysfunctional cerebral autoregulation were not associated with an unfavorable neurologic outcome. Further studies are needed to explore if clinical algorithms targeted to maintain MAP_{OPT} within individualized thresholds improve cerebral oxygenation and neurologic outcomes.

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The University of British Columbia and Clinical Research Ethics Board approved this study protocol. Although deferred consent was initially implemented in many cases, informed consent was obtained from all subjects or their substitute decision-maker.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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