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Cerebrovascular autoregulation following cardiac arrest: protocol for a post hoc analysis of the randomized COMACARE pilot trial

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ABSTRACT:

Background: Approximately two thirds of the mortality following out of hospital cardiac arrest is related to devastating neurological injury. Previous small cohort studies have reported an impaired cerebrovascular autoregulation following cardiac arrest but no studies have assessed the impact of differences in oxygen and carbon dioxide tensions in addition to mean arterial pressure management.

Methods: This is a protocol and statistical analysis plan to assess the correlation between changes in cerebral tissue oxygenation and arterial pressure as measure of cerebrovascular autoregulation, the tissue oxygenation index, in patients following out of hospital cardiac arrest and in healthy volunteers. The COMACARE study included 120 comatose survivors of out of hospital cardiac arrest admitted to ICU and managed with low-normal or high-normal targets for mean arterial pressure, arterial oxygen and carbon dioxide partial pressures. In addition, 102 healthy volunteers have been investigated as a reference group for the tissue oxygenation index. In both cohorts, the cerebral tissue oxygenation was measured by near infra-red spectroscopy.

Conclusions: Cerebrovascular autoregulation is critical to maintain homeostatic brain perfusion. This study of changes in autoregulation following out of hospital cardiac arrest over the first 48 hours, as compared to data from healthy volunteers, will generate important physiological information that may guide the rationale and design of interventional studies.

1. INTRODUCTION

Approximately two thirds of mortality following out of hospital cardiac arrest (OHCA) is related to devastating neurological injury [1]. In contrast, only 10% of OHCA survivors who are discharged from hospital have neurological sequelae that make assistance with activities of daily living necessary [2], while the prevalence of cognitive dysfunction is two to three times higher [3]. The cerebral blood flow (CBF) following return of spontaneous circulation (ROSC) after cardiac arrest typically involves a phase of initial hyperaemia (up to 20 minutes) followed by vasospasm and hypoperfusion (up to 12 hours) and then a gradual return to normal perfusion over 72 hours [4-7]. The phase of hypoperfusion in particular represents a plausible window of opportunity for interventions to support CBF and ameliorate hypoxic ischaemic encephalopathy.

The cerebral arteriolar resistance vessels are instrumental to maintain a homeostatic CBF by cerebrovascular autoregulation (CVAR) and are influenced by mean arterial pressure (MAP), carbon dioxide (P_aCO_2) and oxygen (P_aO_2) levels [8,9]. Several studies have reported an impaired CVAR following cardiac arrest [7,10-13]. An impaired CVAR renders the CBF flow passively pressure dependent and places the brain at risk of hypoperfusion or hyperperfusion as MAP decreases or increases, further compounded by hypoxia/hyperoxia and/or hypocapnia/hypercapnia.

Near infrared spectroscopy (NIRS) can be used to measure cerebral tissue oxygenation ($cStO_2$). The correlations between changes in $cStO_2$ and MAP when analysed as a moving average over short periods of time provide the tissue oximetry index (TOx) (Figure 1). The TOx has been extensively investigated to monitor CVAR in different clinical contexts and it demonstrates a strong correlation with other established technologies to monitor CVAR[14-19] .

In persons with normal CVAR, fluctuations in blood pressure do not cause any immediate marked changes in $cStO_{2,}$ whereas impaired CVAR results in concurrent MAP and $cStO_2$ changes.

The TOx has previously been reported in small cohorts (20 to 51 patients) [10,11,20] of OHCA patients but no studies have assessed the impact of differences in oxygen and carbon dioxide tensions on CVAR during mechanical ventilation in ICU following OHCA. Furthermore, the effects of vasopressor use on CVAR is poorly understood.

The aims of this study are to assess TOx and related variables of CVAR in a large cohort of comatose survivors of OHCA admitted to ICU and managed with low-normal or high-normal MAP, PaO_2 and $PaCO_2$ targets. We aim to characterise changes in CVAR and possible associations with neurological outcome and biomarkers or brain tissue injury. A control cohort of healthy adults (HA) of approximately the same size as the patient cohort will be used to address methodological variability of NIRS derived CVAR and to provide the reference for an ideal, optimal recovery following OHCA. In addition, we aim to typify the timing of impaired CVAR, patient characteristics and cardiac arrest factors associated with impaired CVAR and whether the incidence and severity of CVAR impairment varies according to the target temperature in patients undergoing targeted temperature management (TTM).

2. METHODS

2.1 Study design and populations

This is an observational, multicentre study of data collected prospectively in two independent cohorts referred to as OHCA (Out of Hospital Cardiac Arrest, approved by the ethics committees of the Northern Savo Hospital District, Finland, no. 295/2015, study protocol approved 23.2.2016, this post hoc study approved 12.2.2019, and Midtjylland Region, no. 1-10-72-163-16) and HA (Healthy Adult, approved by the South Western Sydney Local Health District Human Research Ethics Committee, HREC/14/LPOOL/135). No patient identifiable information is maintained in either database and data linkage is only feasible by the running study number reflecting the order of inclusion in the respective databases. Separate individual data files will be compiled for each patient including MAP and $cStO_2$ values that do not include any information enabling identification of the individual patients (such as name, date of birth, initials, any exact dates or time for any event in the database, treating hospital or country).

The OHCA cohort comprises patients admitted to six ICUs in Finland and one ICU in Denmark between March 2016 and March 2017. All patients had a witnessed OHCA of confirmed or suspected cardiac origin with ventricular fibrillation/tachycardia as the initial rhythm, had return of spontaneous circulation (ROSC) within 10-45 minutes but markedly impaired level of consciousness (GCS motor score < 5) and were admitted to ICU for full active management including mechanical ventilation and target temperature management (33-36˚C). Patients with in-hospital CA or CA of non-cardiac origin, non-shockable initial rhythms, no or minimal impairment of consciousness, deemed not for full active management or with an age <18 or >80 years were excluded. The full study protocol and the primary results are published [8,9,21]. The HA cohort comprises adult healthy volunteers studied at

Liverpool Hospital ICU in conjunction with two clinical studies in 2014 and 2017. No participant had any history of cardiovascular or neurological disease or diabetes and refrained from the consumption of nicotine or caffeine on the day of the study. Results for a quarter of the cohort have been published [22].

2.2 Data, calculated variables and outcomes

1. Gender
2. Age, prior health status and functional capacity
3. Cardiac arrest characteristics and resuscitation factors
4. Clinical characteristics in ICU for the first 48 hours
    a. GCS after ROSC
    b. APACHE II score
5. Management in ICU for the first 48 hours
    a. Targeted temperature management including the target temperature
    b. Mean arterial pressure via arterial cannula
    c. Three hourly arterial oxygen tension (P_aO_2)
    d. Three hourly arterial carbon dioxide tension (P_aCO_2)
    e. Frontal cerebral tissue oxygenation ($cStO_2$)
    e. Doses of sedative and vasoactive drugs
6. Cerebrovascular autoregulation
    a. Tissue oxygenation index (TOx)
    b. Optimal tissue oxygenation index (OptTOx)
    c. Mean arterial pressure for optimal tissue oxygenation index (OptMAP)
    d. Upper mean arterial pressure limit for autoregulation (ULA)
    e. Lower mean arterial pressure limit for autoregulation (LLA)

7. Outcome variables

a. Neuron-specific enolase (NSE) at 24 and 48 hours

b. S100B protein at 24, 48 and 72 hours

c. Electroencephalography (EEG) during the first 48 hours

d. Cerebral performance category (CPC) at six months following OHCA

e. Length of stay in ICU

f. Duration of mechanical ventilation

e. Length of stay in hospital

f. Discharge destination

g. Vital status at 30 days following OHCA

Patients in the OHCA cohort were randomised according to a 2^3 factorial design to normal-low and normal-high strata of MAP (65-75 mm Hg vs. 80-100 mm Hg), P_aO_2 (10-15 kPa vs. 20-25 kPa) and P_aCO_2 (4.5-4.7 kPa vs. 5.8-6.0 kPa) as per the pre-published study protocol [21]. Subjects in the HA cohort had MAP manipulated by a randomised sequence of changing bed position, one hand immersed in ice water, mental arithmetic, Valsalva manoeuvre and hand grip manoeuvre.

The $cStO_2$ was measured in both studies by NIRS using bifrontal optodes attached below the hairline and with care taken to avoid the sagittal sinus medially and the temporalis muscle laterally. The mean of the hemispheric readings was used. Mean arterial blood pressure levels over time were measured with variable frequency (2-10 minutes). The moving Pearson correlation coefficient between $cStO_2$ and MAP as measured at ten minutes intervals for the first 48 hours after admission to ICU will be analysed to generate TOx as previously described [19]. The TOx approaches a range of 0 to -1 to indicate intact CVAR, and a range of

0 to 1 to indicate impaired CVAR. Mean tissue oximetry index values will be derived for the first 0-12 hours in ICU and then for the periods of >12-24 and >24-48 hours.

The TOx is categorised into MAP bins of 5 mmHg and fitted to a second-order polynomial curve to calculate OptTOx and the OptMAP, i.e. the point of the most negative TOx indicating an optimal CVAR and the corresponding MAP (Figure 1). The MAP corresponding to a TOx threshold of 0.30[17] will be calculated to represent the lower (LLA) and upper (ULA) limits of autoregulation, and to calculate the range of intact autoregulation (LLA-ULA) (Figure 1). The weighted multi-window method proposed by Depretiere et al. [23] will be used in which multiple calculation windows are applied during a time frame ranging from 1 h to the total length of the recording (in 10 min increments) for each period above. A weighted average is calculated for each parameter (OptTOx, OptMAP, LLA, ULA and range) and will be reported for each period. Calculations of CVAR indices is performed using the ICM+ Brain Monitoring software (Version 8.3, University of Cambridge, Cambridge, UK).

2.3 Outcomes

The primary outcome is the comparison of changes in CVAR assessed by TOx against neurological outcome. The secondary outcomes include changes in biomarkers and extent of resource utilisation compared to changes in OptTOx, OptMAP, ULA, LLA and range. Both primary and secondary outcomes are explored in the groups according to the 2^3 design for MAP, P_aO_2 and P_aCO_2 targets in OHCA. The feasibility outcomes compare the CVAR indices in OHCA against HA to investigate methodological variability and the degree of separation in CVAR between OHCA and HA subjects.

2.4 Samples size and power

The OHCA cohort comprises 120 patients and the HA cohort comprises 102 subjects with all data capture procedures concluded. No formal sample size calculation has been performed specific to this protocol. The concentration range for biomarkers, the duration range for resource variables and the number of patients dying or with a poor neurological outcome according to the primary publications [8,9] are sufficient to allow for multiple CVAR variables to be included in regression analyses [24,25]. All analyses in this observational study of already prospectively collected data will be considered exploratory and hypothesis-generating only.

2.5 Statistics.

Data will be presented as appropriate for categorical and normally or non-normally distributed variables based on the D'Agostino-Pearson omnibus normality test. Patient characteristics and outcomes will be reported according to the original 2^3 factorial design with the CVAR indices separately for 0-12, >12-24 and >24-48 hours. A threshold of mean TOx >0.3 to indicate impaired CVAR at 0-12, >12-24 and >24-48 hours will be used to compare any differences in NSE, S100B, length of stay in ICU and in hospital using Student's t-test and Mann-Whitney U test as appropriate. The CVAR indices will be separately reported for the dichotomous outcomes of NSE at 48 hour above or below the Youden index-based best cut-off value to predict poor neurological outcome in the COMACARE study, CPC1-2 vs. CPC 3-5 at six months, dead vs. alive at 30 days and mildly vs. moderately/severely abnormal EEG for 48 hours using receiver operating characteristics. We will also compare the incidence of CVAR in patient treated with TTM targeting 33°C (83 patients) compared to those targeting 36°C (37 patients). A multivariable model will be created with factors available on hospital admission aiming at predicting the development of CVAR.

The associations between CVAR indices and continuous outcomes as dependent variables will be analysed by multiple linear regression with TOx and OptTOx included a priori. Multicollinearity will be assess using a variance inflation factor >3. The fit of the model will be reported by the F statistic and its P value and any independent variables will be reported by the unstandardized regression coefficients (B), their 95% confidence interval and P values.

Associations between CVAR indices and dichotomous outcomes as dependent variables will be analysed by binary logistic regression analyses with TOx and OptTOx included a priori. The goodness of fit of the model using the Hosmer-Lemeshow test will be reported as well as the odds ratios and their 95% confidence intervals for any independent variables.
A two-tailed P value <0.05 will be used to indicate statistical significance with appropriate corrections for multiple comparisons. All statistical analyses will be performed using the latest version of the SPSS statistical package (IBM Corporation, Armonk, NY, USA).

2.6 Missing data

The HA database contains no missing data and the degree of missing values in the OHCA database will be reported. Physiologically impossible values will be classified as missing and analyses based on the most complete datasets possible. No imputations for missing data will be performed.

2.7 Reporting

The results will be submitted to a peer-reviewed, international journals with a focus on the management of cardiac arrest patients in the ICU. The results will be reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE)

statement [26]. This protocol has been developed as far as possible to comply with the STROBE statements and the reporting of diagnostic accuracy studies [27].

3. DISCUSSION

The NIRS technique to monitor CVAR holds clinical promise as it is continuous, non-invasive and available at the bedside. With the assumption that other influences such as cerebral metabolic rate, haematocrit and oxygen diffusivity do not vary over short periods of time the $cStO_2$ measured by NIRS serves as a surrogate measure of CBF. As a result, changes in $cStO_2$ changes when correlated to changes in MAP allow the monitoring of CVAR. While the technique has been extensively reported, and validated against other methods to assess CVAR, monitoring CBF and the integrity of CVAR is not routinely applied in most ICUs managing OHCA patients. There is hence a limited body of evidence regarding NIRS to assess CVAR in comatose survivors of cardiac arrest admitted to ICU and the present study cohort is two to six times larger than any previously published and conducive to a comprehensive analysis of factors known to influence CVAR.

The CBF following cardiac arrest is known to be variable at different points in time relevant to management in ICU. In patients with relatively intact CVAR following OHCA the upper limit of autoregulation is typically right-shifted meaning that a 'normal' MAP might still be insufficient to sustain CBF. Furthermore, the CVAR appears more effective above the upper limit of autoregulation compared to below the lower limit of autoregulation [28]. There is a strong argument but limited evidence to individualise MAP targets in managing OHCA patients and this study aims to address this knowledge gap. An important feature of this study using NIRS is the assessment of CVAR rather than the $cStO_2$ *per se*, *since* the $cStO_2$ in itself does not appear to be associated with markers of neurological injury or outcome [29]. The

median frontal $cStO_2$ values were not different in the primary reports from the OHCA cohort [8,9]. A recent study of 57 acutely comatose patients with a variety of neurological injuries admitted to a neurocritical care unit demonstrated that TOx correlated with GCS and the GCS motor score whereas the $cStO_2$ value did not [30].

The premise of this study is that indices of CVAR will vary between patients with varying degrees of neurological insult inflicted by cardiac arrest and resuscitation as measured by biomarkers, resource utilisation and patient centred clinical outcomes. Not only will the overall CVAR capacity as monitored by TOx be assessed but also the MAP for the optimally effective TOx. If it is accepted that the OptMAP represents an ideal individualised MAP target, this study enables a quantitative analysis of the importance of deviations from OptMAP during the time periods assessed. Better neurological outcomes defined by Glasgow Outcome Score were demonstrated when cerebral perfusion pressure was maintained close to OptMAP in an interventional study in head injured patients [31]. In addition, the delineations of the LLA and ULA allows for a similar quantitative assessment of the time spent within and outside these limits in relation to the study outcomes. Previous studies have indicated that cerebral hyperaemia induced by a MAP above the ULA is associated with the development of delirium following cardiac surgery using cardiopulmonary bypass [32,33]. While this study protocol cannot establish any causality between changes in CVAR and outcomes, any associations demonstrated may inform the design of future interventional studies.
The inclusion of the HA cohort as a comparator is important to highlight the magnitude of CVAR changes observed in OHCA patients. The methodological issues and inherent variability for NIRS derived indices of CVAR have previously been contrasted to healthy subjects in a limited fashion [10]. Comparisons of the OHCA and HA cohorts enable the

calculation of plausible effect estimates if CVAR indices would be targeted as primary outcomes in an interventional study.

3.1 Limitations and strengths.

Enrolment into the OHCA cohort was based on pre-published inclusion and exclusion criteria[21] with less than ten percent of screened patients excluded for other reasons. The risk for selection bias in patients is hence deemed negligible. The NIRS monitoring was performed blinded to ICU staff and all CVAR calculations are performed off-line and post-hoc and hence the risk for indication bias is considered insignificant. The much greater number of patients included compared to previous studies is conducive to assessing the variability of CVAR observed following OHCA and hence any spectrum bias is minimised. While the proprietary algorithms to generate $cStO_2$ make direct comparisons using different NIRS monitors difficult[34], the calculated correlation based on relative changes in $cStO_2$ and MAP is considered less dependent on equipment and thus any classification bias is negated. All calculations of CVAR indices will be performed blinded to outcome data to minimise the risk for outcome bias. The statistical analyses will be performed by an independent biostatistician blinded to the outcomes of interest.

4. CONCLUSION

Cerebrovascular autoregulation is critical to maintain homeostatic brain perfusion. This study of changes in autoregulation following out of hospital cardiac arrest over the first 48 hours, as compared to data from healthy volunteers, will generate important physiological information that may guide the rationale and design of interventional studies.

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