Cerebral Oximetry as a Biomarker of Postoperative Delirium in Cardiac Surgery Patients

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ABSTRACT

Purpose: A promising monitoring strategy for delirium is the use of cerebral oximetry, but its validity during delirium is unknown. We assessed the relationship between oximetry and delirium. We hypothesized that as cerebral oximetry values increased, delirium would resorb.

Materials and Methods: An observational study was conducted with 30 consecutive adults with delirium following cardiac surgery. Oximetry, delirium assessments and clinical data were collected for three consecutive days following delirium onset. Oximetry was obtained using near-infrared spectroscopy. Delirium was assessed using diagnosis, occurrence (Confusion Assessment Method-ICU) and severity scales (Delirium Index).

Results: All patients presented delirium at entry. The mean oximetry value decreased from 66.4 ± 6.7 (mean ± standard deviation) to 50.8 ± 6.8 on the first day following delirium onset and increased in patients whose delirium resorbed over the three days. The relationship between oximetry, delirium diagnosis and severity was analyzed with a marginal model and linear mixed models. Cerebral oximetry was related to delirium diagnosis ($p \leq 0.0001$) and severity ($p \leq 0.0001$).

Conclusion: This study highlighted the links between increased cerebral oximetry values and delirium resorption. Oximetry values may be useful in monitoring delirium progression, thus assisting in the management of this complicated condition.

Keywords:

Cerebral Oximetry, Spectroscopy, Near-Infrared, Delirium, Thoracic surgery, Postoperative Complications.

INTRODUCTION

Background

Delirium following cardiac surgery is not always avoidable and its length and severity are associated to mortality and long-term cognitive impairment[1]. The American Psychiatric Association recommends that delirium assessment in clinical practice is best achieved when medical diagnosis is supplemented with observational assessment tools [2]. The gold standard in practice is the Confusion Assessment Method (CAM), which has been validated among intensive care patients with the CAM-Intensive care unit (CAM-ICU)[3]. Other tools have been validated as well; the Intensive Care Delirium Screening Checklist (ICDSC) provides information on the occurrence of delirium while the Delirium Index (DI) informs on severity[4, 5]. The use of these tools leads to enhanced delirium assessment when compared to clinical judgment alone[6]. However, delirium monitoring in current practice remains suboptimal.

A promising strategy is the use of biomarkers, which can support delirium monitoring without relying solely on observing manifestations. Brain oxygen saturation (cerebral oximetry), reflecting the balance between oxygen delivery and consumption, is promising. This measure also reflects cerebral blood flow, a possible contributing factor of delirium[7]. Therefore, cerebral oximetry could be used to highlight an internal process occurring during delirium. Near Infrared Spectroscopy (NIRS) is a non-invasive device that measures oximetry. Previous studies have reported an association between enhanced preoperative and intraoperative cerebral oximetry and the lower risk of postoperative delirium. However, regular measurement of cerebral oximetry during delirium has not been

reported. Hence, it is still unclear whether this tool is valid.

In the present study, we assessed the concurrent validity of oximetry in monitoring delirium reflected by the relationship between oximetry values and the occurrence and severity level of delirium as measured by validated tools. Oximetry values were measured at the cerebral and peripheral area using NIRS technology. Because we wanted to control for decrease in cerebral oximetry due to hypoperfusion reasons, we also measured peripheral oximetry values. Occurrence of delirium was measured using the medical diagnosis and the CAM-ICU and severity of delirium was measured using the DI. We hypothesized that higher cerebral oximetry values would decrease the odd of delirium occurrence while peripheral oximetry values would not. Additionally, we hypothesized that higher cerebral oximetry values would be related to lower severity level of delirium while peripheral oximetry values would not.

MATERIALS AND METHODS

Definition of Delirium

In our study, delirium is defined by a score of four or more on the Intensive Care Delirium Screening Checklist (ICDSC), matched with a medical diagnosis in the medical chart[4]. The ICDSC is described in the Variable and Data Measurement Section.

Study Design and Setting

The present observational study is embedded in a pilot randomized controlled trial (RCT) which's primary aim was to examine the acceptability and feasibility of a nursing intervention of delirium management[8] (Controlled Trials #ISRCTN95736036). The

study's secondary objective, which is presented in the present paper, was to assess the concurrent validity of cerebral oximetry as an indicator of delirium by examining its relationships with occurrence and severity level of delirium. The study was conducted in an ICU and surgery ward from a Canadian tertiary cardiology university hospital. Approval was obtained from the research center's ethics and scientific committee. The design and data collection sequence is presented in Table 1.

Participant Selection

All eligible patients had to have delirium for study entry. This particularity called for the use of surrogate consent to participate in research, during the time when the patient was temporarily inapt. This implied that a family caregiver had to consent for study entry, before consent could be confirmed with the patient after delirium.

Eligibility criteria. The inclusion criteria were 1) To present post-surgery delirium; 2) To have had either coronary artery bypass grafting (CABG) or heart valve surgery; 3) To have a family member present to consent within 24 hours after delirium onset; 4) To have no planned transfer to another hospital within the three days following delirium onset; 5) To have the preoperative cognitive ability to confirm the surrogate consent provided by the family caregiver after delirium resolution and speak and read French. 6) To have the potential of recovering full cognitive ability following surgery, example: not presenting a diagnosis of delirium superimposed on dementia affecting cognitive abilities.

Selection of the sample. Assessment for eligibility was performed in two steps. Step one consisted of targeting patients who presented postoperative delirium (eligibility criteria #1**).** Step two was performed only among patients with delirium and consisted of

assessing eligibility on the remaining criteria. The patient was entered in the study when his family caregiver gave consent during delirium and once delirium had resolved, the patient's informed consent was obtained.

Variables and Data Measurement

Oximetry assessment. Assessments for oximetry using the Invos 5100 were performed by the principal investigator (TM) trained by the anesthesiologist/intensivist investigator (AD).

Oximetry values were obtained using the INVOS 5100 device (COVIDIEN, Somanetics Corporation). In the present study, one optode (Invos adult SomaSensors, COVIDIEN, Somanetics Corporation) was used per patient (the same for three days) and before each measuring sequence functioning of optodes was verified on the investigator's arm. Following this, the optode was consecutively placed on four different sites on the forehead as represented by areas 1, 2, 3 and 4 of Figure 1. Then, the optode was placed on one arm and one leg on either the right (5a and 6a on Figure 1) or the left (5b and 6b on Figure 1) side. On each site, the optode was left in place for 20 seconds or until signal stability, after which the value appearing on the device was retained. From the six oximetry values (four cerebral, one arm and one leg), we calculated two mean scores: a cerebral mean score based on the four sites on the forehead (1, 2, 3 and 4), and a peripheral score based on the one arm and the one leg (5a and 6a or 5b and 6b). These are treated as continuous variables.

Delirium assessment.

Delirium screening in usual care. The ICDSC consists of an eight item scale based on the DSM-IV-TR. The items include altered level of consciousness, inattention,

disorientation, hallucination, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbance and symptom fluctuation[4]. The score ranges from 0 to 8[4]. The ICDSC sensitivity and specificity are respectively 0.94 and 0.64[9]. In the research setting the ICDSC is completed as part of usual care three times a day plus as needed. It is completed by bedside nurses when the patient's level of consciousness allows for assessment.

Delirium tools for hypothesis testing. In addition to the ICDSC and the medical diagnosis, two validated observational assessment tools were introduced for the present study i.e. the CAM-ICU and DI. This assessment was performed by the bedside nurse with minimal training and clarifications from the PI (TM) when necessary.

The CAM-ICU consists of a four-item algorithm, based on the DSM-IV[3]. These items include a sudden appearance of (1) change in mental status or a fluctuation in this state, (2) inattention, (3) disorganized thinking and (4) altered level of consciousness. The occurrence of delirium reflected by a positive score on the CAM-ICU (CAM-ICU+) is determined by the presence of the first two items combined with the third or fourth item; otherwise, the CAM-ICU is negative (CAM-ICU-)[3]. The CAM-ICU's sensitivity ranges from 0.95 to 1.00 and its specificity from 0.89 to 0.93[3].

The Delirium Index (DI) consists of a seven-item scale, based on the DSM-IV and was selected among other severity tools because it was relevant for an ICU setting potentially involving intubated patients[5]. These items include (1) inattention, (2) disorganized thinking, (3) altered level of consciousness, (4) disorientation in time and place, (5) memory impairment, (6) perceptual disturbances and (7) hyperactive of hypoactive psychomotor. Each item can be rated from 0 to 3 and the total possible score

for the DI ranges from 0 to 21, higher scores reflecting a higher level of delirium severity. The reported alpha coefficient ranges from 0.74 to 0.82 and inter-rater reliability is 0.98[10].

Synchronization of Measures Related to Hypothesis Testing. We used the first ISDSC identified during step one of recruitment as the reference starting point. The measures of delirium (CAM-ICU and DI) and oximetry values were performed within 24 hours of the reference starting point (day 1) and then daily for two consecutive days, thus days 2 and 3. Oximetry and delirium measures were collected within a one-hour time frame.

Clinical Data. Relevant clinical data as potential covariates was collected from medical records. These possible covariates were selected from the literature and clinical practice, for the potential influence on either oximetry values and/or delirium assessment[11, 12]. Coding and definitions of each variable are described in Tables 2 to 5 and are based on previous work[13].

The study patients' sociodemographic characteristics were described with age, skin color and gender. The baseline clinical data were described with variables referring to either pre-existing comorbidities (Body mass index, cardiac operative risk, hypertension, dyslipidemia, chronic kidney disease, Type 2 diabetes, past depression episode and past cerebrovascular accident) or delirium risk factors (intraoperative baseline oximetry, need for visual or auditory aid, tobacco or alcohol consumption, previous delirium episode, pre-existing cognitive impairment).

The participant's surgical and postoperative characteristics were described using the following variables: urgency of surgery and type of surgical procedure. Additional surgical characteristics variables include: cardiopulmonary bypass time, clamp time,

intraoperative desaturation in cerebral oximetry, intubation length, positive fluid balance at the end of surgery and ventricular function. Additionally, the post-procedure events that occurred before delirium onset were also described with positive fluid balance during ICU stay, the occurrence of acute kidney injury, infection, cerebrovascular accident and re-intubation. Finally, ICDSC scores at delirium onset, medical diagnosis of delirium at onset and postoperative day of delirium onset were also collected.

Description of the clinical data at days 1, 2 and 3 following delirium onset was achieved using the following time-dependent variables: systolic and diastolic blood pressures, pulse oximetry, temperature, hemoglobin, creatinine, oxygen supply, positive fluid balance during delirium, psychotropic medication and finally medication that could influence NIRS values, i.e.: antiarrhythmic, sympathomimetic, vasodilator or anti-hypertensive medication.

In addition to the measures of oximetry and delirium at days 1, 2 and 3, we also collected the diagnosis of delirium and the type of delirium related manifestation of either hypoactive versus hyperactive as noted on the Delirium Index scale at the time of data collection.

Study Size

This observational study sample size of 30 patients involved three measurement points, resulting in a possible maximum of 90 measuring points. The sample size was determined by the pilot RCT in which it was embedded and no statistical power was calculated before conducting the study.

Statistical Analysis

Continuous variables are presented as means ± standard deviations and categorical

variables are presented as frequencies and percentages.

The study participants flow was described using descriptive analyses. To address potential selection bias, we compared four characteristics (age, gender, surgery type and ICDSC score) of the delirious patients included versus those excluded on the second step on the basis of criteria detailed in the Participant Selection section.

To ascertain that the measures obtained from the four cerebral oximetry sites would be well represented by a mean score, we first used Pearson r to describe the correlation between these four sites. The same was done for the one arm and one leg peripheral sites. Thereafter, two mean scores were calculated from the oximetry measuring sites represented on Figure 1.

The concurrent validity was expressed via the relationship between oximetry values and occurrence and severity level of delirium. These relationships were analyzed by making use of marginal models (MM) and linear mixed models (LMM) respectively, while controlling for time, sociodemographic and clinical data. All clinical data mentioned in the Variables and Data Measurement sections were entered in the models in a forward stepwise approach. A repeated-measures design was used. Such model permits the data to exhibit correlations and non-constant variances over time and provide the flexibility of modeling not only the means of the data but also their variances/covariances or correlations. Due to the small sample size, a forward approach was used to select covariates.

Time-independent (e.g., gender) and time-dependent (e.g., blood pressure) independent variables were considered. Random components (e.g., intercepts, slopes) were introduced and tested to depict individual trajectories over time when using LMM. Generalized estimating equations (GEE) and a restricted maximum likelihood (REML)

approach were used to estimate the coefficients for the marginal models (CAM scores) and the linear (DI scores) mixed models respectively. The examination of residuals did not show any problem associated with non-linearity, non-normality or outliers. All statistical analyses were performed using SPSS, version 21.0, SPSS Inc., Chicago, USA. The significance level was set at 0.05 for all tests.

RESULTS

Participant Flow. The sample of 30 patients was enrolled from July 2013 to June 2015. Of the 2735 patients who underwent cardiac surgery during the study period 441 (16%) presented delirium. Among these 441 patients with delirium, 30 were included. The others (n=411) not meet the inclusion criteria because there were no family members present to consent within 24 hours following delirium onset (n=214) or they had a planned transfer to another hospital (n=96), did not undergo CABG or valve surgery (n=22), did not meet the preoperative cognitive ability or language requirement (n=31) or the postoperative potential to recover cognitive ability (n=14), refused (n=9) or were excluded because of logistical issues (n=25).

We contrasted the 30 delirious patients included in our study to the 411 patients who presented delirium but were excluded on the basis of the other criteria presented in the Participant Selection section. Mean age (75.3 ± 7.9 vs 71.60 ± 9.3) and mean ICDSC score at delirium onset (4.7 ± 1.4 vs 4.6 ± 1.1) were similar in included and excluded patients respectively. Male gender representation (63.3% vs 69.8%) and heart valve surgery (60% vs 53.3%) were also similar in these two groups respectively.

Descriptive Data.

Characteristics of study patients. As shown in Table 2, the patients were mostly

male and aged an average of 75 years old with hypertension (86.7%), dyslipidemia (80%) and chronic kidney disease (43%) preoperatively. The most frequent delirium risk factors were the need for auditory and/or visual aid (100%) and tobacco or alcohol consumption (43.3%).

Table 3 summarizes the surgical and postoperative characteristics which occurred before delirium onset. Surgical procedures were more often elective than urgent in the present sample and for heart valve than CABG. Following the surgical procedure, but before delirium, half had positive fluid balance ≥ 2 liters and 23% developed acute kidney injury stage ≥ 1 on the Acute Kidney Injury Network classification[14]. Finally, all patients had scores of 4 or more on the ICDSC and a medical diagnosis of delirium at onset, which occurred within three days following the surgical procedures for 60% of the patients.

Table 4 summarizes the variables collected at day 1, 2 and 3 after delirium onset. Vital signs were generally within the normal range. For all three days following delirium onset, the mean hemoglobin levels were low when compared to normal values, but all were above 70 gm/L, while around half the sample had high creatinine levels (up to 60%). Within clinical potential covariates that could affect oximetry measures during days 1 to 3, up to 46% received some oxygen supply from nasal cannula or oxygen mask. Up to 57% received some psychotropic medication two hours prior to delirium assessment from day 1 to day 3. Finally, up to 40% received any dose of medication that could influence NIRS values within two hours prior to the oximetry assessment from day 1 to day 3.

Study variable data. For the oximetry measures, the Pearson coefficient varied from 0.568 to 0.906 ($p < 0.01$) between the four cerebral oximetry sites and from 0.721 to 0.781 ($p \leq 0.0001$) between the two peripheral oximetry sites (one arm and one leg). Mean

scores for cerebral and peripheral oximetry were therefore used in the analytical model.

As reported in Table 5, the mean cerebral oximetry values varied from 50 to 54% from day 1 to 3 while the mean peripheral oximetry values were 67%. For delirium related variables, 28 patients had a medical diagnosis of delirium matched with CAM-ICU positives on day 1, 17 on day 2 and 8 on day 3 indicating that delirium resolved as the days passed for some patients. Although all patients were diagnosed with delirium at study entry, for 2 patients the diagnosis and CAM-ICU score were negative on Day 1 following delirium onset indicating the symptoms of delirium were resolved within 24 hours of study enrolment.

Main Results.

In the marginal models (Table 6), results were in line with our hypotheses. For Hypothesis 1, higher cerebral oximetry values decreased the odd of delirium occurrence (odds ratio (OR) 0.73, $p < 0.001$). For hypothesis 2, we observed that peripheral oximetry values did not affect the odds of delirium occurrence (OR 1.01, $p = 0.871$). The relationship between oximetry values and delirium was not altered by controlling for all potential co-variables tested separately. The only covariate that remained significant was acute kidney injury in the peripheral oximetry model which increased the odd of delirium occurrence by close to 4 (OR 3.97, $p = 0.041$). Finally, as time goes by, the odd of delirium occurrence decreases in both the cerebral and peripheral marginal models (OR ≤ 0.25, $p < 0.001$).

In the two LMM models, results were also in line with our hypotheses. For Hypothesis 3, higher cerebral oximetry values were negatively related to lower levels of delirium severity ($p < 0.001$). For Hypothesis 4, peripheral oximetry values were not related to severity level of delirium ($p = 0.595$). In these LMM models, the relationship

between cerebral oximetry and delirium was not altered by controlling for all potential covariates. Hemoglobin remained a significant variable in both the cerebral ($p = 0.013$) and peripheral ($p = 0.037$) oximetry LMM model. Additionally, positive fluid balance during ICU stay remained a significant variable in the peripheral oximetry LMM model ($p = 0.008$). Finally, we observed that, as time goes by, levels of delirium severity level decreases ($p < 0.001$).

DISCUSSION

Key results.

We found cerebral oximetry to be related to the occurrence and severity of delirium, while peripheral values were not. Due to lack of previous data, no statistical power calculation was performed. However, having observed significant associations between oximetry and delirium with the linear mixed model and the marginal model, we may conclude that we had sufficient power to detect these important effects. Although observed in a small sample, these relations were affected by the inclusion covariates in the analyses. The covariate of acute kidney injury following surgery, but before delirium onset, remained statistically significant in the marginal model testing the relation between peripheral oximetry and occurrence of delirium. In the linear mixed model (LMM) of the relation between both cerebral and peripheral oximetry values and severity level of delirium, the covariate hemoglobin levels on days 1, 2 and 3 following delirium onset remained significant, while positive fluid balance during ICU stay but before delirium onset was significant only in the peripheral oximetry model. Not surprisingly, in all models, as the time passed, the occurrence and severity of delirium decreased.

Limitations

Limitations include a small sample size of patients who all presented delirium at study entry. Our delirium and cerebral oximetry assessments were performed once daily, not continuously, making it possible to have missed periods of more or less severe delirium manifestations. Finally, as the CAM-ICU was not part of usual care, bedside nurses could consult the primary investigator who was collecting cerebral oximetry data to clarify or validate their understanding of the scales.

Potential selection bias. Recruitment challenges experienced in our study were the result of low prevalence of delirium in addition to constraints of needing a family member to consent. The prevalence of 16% observed in our study was much smaller than previous studies in which from 30 to about 55% of critical care patients presented delirium [15, 16].

The potential for a selection bias was address by contrasting the patients with delirium who were included in our study to those who were excluded. Although some small differences in terms of age and surgery type, our sample of 30 was a somewhat fair representation of patients with delirium in the research.

Confounding. NIRS used in this study to calculate oxygen concentration rely on penetrating the skull and having near infrared light absorbed by oxyhemoglobin and desoxyhemoglobin, its calculation of oxygen concentration in the brain could be affected by anatomical differences, skin color, adipose tissues, low hemoglobin levels and bilirubin levels[11, 17]. In the present study, we controlled for these potential differences by including adipose tissues (as reflected by BMI) and hemoglobin levels and the results remained conclusive. As all our patients were Caucasian, skin color was not an issue in the present sample.

Previous studies.

Low pre and intra-operative cerebral oximetry are predictors of post-operative delirium in cardiac surgery settings[18-20]. Earlier work supports the link between delirium and cerebral blood flow disruptions[7, 21, 22]. A reduction in cerebral blood flow during delirium has been measured in previous studies with different neuroimaging techniques, for example single-photon emission computed tomography[7, 21, 22].

Taussky and colleagues suggests that cerebral oximetry obtained with NIRS is an indicator of cerebral blood flow and multiple studies have supported this finding[23, 24]. Therefore, the link between cerebral oximetry and delirium is explained, at least partially, by a disruption of cerebral blood flow and cerebral autoregulation disruptions.

To our knowledge the present study is the first to report on the evolution of cerebral oximetry during post cardiac surgery delirium. In other populations, Pfister and colleagues compared cerebral oximetry in 12 patients with sepsis-related delirium versus 4 without delirium and found a statistically significant difference in cerebral autoregulation, but not in cerebral perfusion measured with transcranial Doppler and NIRS[25]. Reasons why NIRS results did not differ between delirious versus not delirious patients in Pfister et al's study, whereas this difference was observed in the present study, could be explained by divergent methodological factors. These factors include the population of patients with sepsis versus our postoperative clientele, the sample size, the sites, the amount and the timing of NIRS measurement.

Covariates

Another important finding relates to the stability of the relationships between oximetry and occurrence and severity of delirium, while controlling for relevant clinical

covariates. Most of the tested covariates were not statistically significant.

Hemoglobin and positive fluid balance were thought to be related to the measurement of oximetry. The NIRS' ability to measure tissue oximetry relies on the light absorption properties of hemoglobin that differs depending on the presence or absence of oxygen. Therefore, the oximetry reading could be affected by low hemoglobin levels[11, 17]. A similar assumption was made for the variable of positive fluid balance, because higher interstitial liquid associated with higher venous pressure could alter oximetry readings. This is consistent with the reported association of positive fluid balance, delirium but also acute kidney injury from congestion[26].

The covariate of acute kidney injury (AKI) was tested for its indirect impact on consciousness and delirium via the accumulation of toxic metabolites leading to disruption of cerebral microcirculation[27]. AKI increased the occurrence of delirium but did not alter the relationship between cerebral oximetry and occurrence of delirium.

The main message emerging from our results is that low cerebral oximetry, even in patients who developed AKI, positive fluid balance or with lower hemoglobin concentration, are indicative of delirium occurrence and severity possibly because it reflects cerebral blood flow disturbances.

CONCLUSION

Measuring cerebral oximetry stands out as an alternative avenue that can be used to monitor delirium. Assessment of oximetry during delirium was feasible in this clientele with whom the use of classical neuroimaging techniques, which often require moving the

patient, is challenging. Finally, larger studies should be conducted to corroborate and compare our observations as cerebral oximetry might be key in enhanced monitoring of delirium.

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Conflict of Interest:

None declared.

Figure Legend

Figure 1 – Oximetry measurements sites

Oximetry values were collected at six different sites on the body and these include all cerebral sites (1, 2, 3 and 4) in addition to one arm and one leg (5a and 6a OR 5b and 6b).

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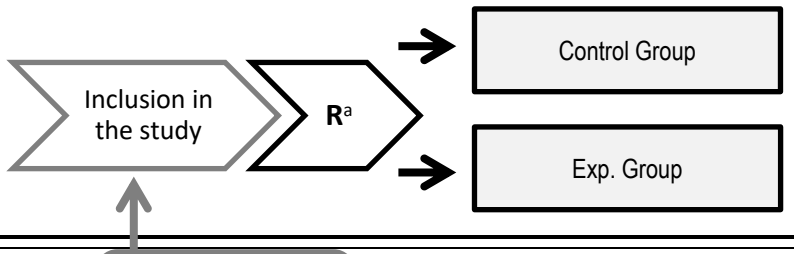
TABLES AND FIGURES

Table 1. Observational study design within the main pilot-RCT.

PILOT STUDY TIMELINE



OBSERVATIONAL STUDY TIMELINE	***Pre-surgery***	***Surgery***	***Post-surgery***	***Delirium onset***	***Delirium day 1 (T1)***	***Delirium day 2 (T2)***	***Delirium day 3 (T3)***
Outcome Assessment:							
Sociodemo-graphic data	●	●	●				
Clinical data	●	●	●	●	●	●	●
Delirium Assessment:							
CAM-ICU					●	●	●
ICDSC					●	●	●
DI				●	●	●	●
Oximetry Assessment [b]:							
INVOS 5100					●	●	●

Template adapted from the SPIRIT guidelines[28]; ● Data collection in the study; [a] R : Randomization; [b] Oximetry assessment is performed using the INVOS 5100 Near Infrared Spectroscopy device (COVIDIEN, Somanetics Corporation).

Table 2. Sociodemographic and baseline clinical data (N=30)

	***n* (%) or mean ± standard deviation (min-max)**
Sociodemographic characteristics	
Age, *Years*	75.3 ± 7.9 (59-89)
Skin color, *White*	30 (100)
Gender, *Male*	19 (63.3)
Pre-existing comorbidities	
Body mass index, *Kg/m²*	28.1 ± 5.3 (18.8 – 38.1)
Cardiac operative risk [a] (EuroSCORE II)	4. 5 ± 4.4 (0.9 – 21.4)
Hypertension [b], *yes*	26 (86.7)
Dyslipidemia [b], *yes*	24 (80)
Chronic kidney disease [c] , *yes*	13 (43.3)
Type 2 diabetes [b], *yes*	10 (33.3)
Past depression episode [b], *yes*	10 (33.3)
Past cerebrovascular accident, *yes*	4 (13.3)
Delirium risk factors	
Preoperative Oximetry [d] , %	66.4 ± 6.7 (53.5 – 79.5)
Need for auditory or visual aid, *yes*	30 (100)
Tobacco or alcohol consumption, *yes*	13 (43.3)
Previous delirium episode, *yes*	5 (16.7)
Pre-existing cognitive impairment, *yes*	0 (0)

[a] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) online calculator was used (http://www.euroscore.org/calc.html). [b] A condition that was diagnosed and medically treated. [c] The Renal Association's chronic kidney disease (CKD) stage classification was used. Patients with stages 3 and higher scored positive for CKD (http://www.renal.org). [d] n = 23, missing data attributed to the fact that retaining cerebral oximetry values during surgery is not systematically performed by all anesthesiologist in the study center.

Table 3. Surgical and postoperative characteristics (N=30).

	***n* (%) or mean± standard deviation (min-max)**
Surgical procedure	
Urgency of surgery [a], *yes*	
Elective	20 (67)
Urgent	10 (33.3)
Type [b], *yes*	
Heart valve	18 (60)
Coronary artery bypass graft	12 (40)
Cardiopulmonary bypass time [c], *Minutes*	80. 8 ± 29.3 (33 - 142)
Clamp time [c], *Minutes*	60 ± 26.7 (22 - 126)
Desaturation in cerebral oximetry [d], *yes*	12 (40)
Immediate post-procedure characteristics	
Intubation length	
≤ 12 hours	21 (70)
> 12 hours	9 (30)
Positive fluid balance of ≥ 2 liters at the end of surgery [e, f], *yes*	16 (53.3)
Ventricular function [g], *abnormal*	22 (73)
Post-procedure events before delirium	
Positive fluid balance of ≥ 2 liters during ICU stay [f], *yes*	15 (50)
Acute kidney injury [h], *yes for Stage ≥1*	7 (23.3)
Infection [i], *yes*	4 (13.3)
Cerebrovascular accident, *yes*	2 (6.7)
Re-intubation [j], *yes*	1 (3.3)

Post-procedure event of delirium	
Onset	
ICDSC score at delirium onset	
score = 4	17 (56.7)
score ≥ 5	13 (43.3)
Medical diagnosis of delirium at onset, *yes*	30 (100)
Postoperative day of delirium onset	
≤ 3 days	18 (60)
> 3 days	12 (40)

[a] For urgency of procedure we used the definition proposed in the EuroSCORE assessment (http://www.euroscore.org/calc.html).[b] "heart valve" : alone or as a primary surgery but CABG added, and "coronary artery bypass graft": alone or as a primary surgery but valve surgery added, [c] n=27, missing data attributed to some surgical techniques did not require pump circulation (two patients under CABG on beating heart and one patient had valve surgery with trans-catheter aortic valve implantation (TAVI). [d] n=23, missing data attributed to the fact that retaining cerebral oximetry values during surgery is not systematically performed by all anesthesiologist in the study center. [e] Positive liquid in/out balance of ≥ 2 liters in 24 hours. [f] n=29, missing data related to the fact that this information was not included in the medical chart for one patient. [g] Abnormal ventricular function was determined to be an abnormal left ventricular ejection fraction value and an abnormal diastolic left ventricular function values obtained assessed intraoperatively with transesophageal echocardiography. [h] Stages were determined using the Acute Kidney Injury Network (AKIN) classification[14]. [i] Infection treated with antibiotics. [j] Novel intubation following initial postoperative extubation.

Table 4. Clinical data at days 1, 2 and 3 following delirium onset.

	***n* (%) or mean± standard deviation (min-max)**		
	Day 1 (n=30)	**Day 2 (n=30)**	**Day 3 (n=28)**
Systolic blood pressure, *MmHg*	123.7 ± 16.7 (95-160)	125.13 ± 15.49 (100-159)	126.50 ± 18.53 (99-170)
Diastolic blood pressure, *MmHg*	58.9 ± 11.2 (35-76)	60.13 ± 11.81 (34-81)	62.57 ± 10.97 (49-85)
Pulse saturometry, *%*	94.9 ± 2.4 (91-100)	95.80 ± 2.657 (91-100)	96.46 ± 2.168 (93-100)
Temperature, $^{\circ}C$	37 ± 0.6 (35.90 – 37.90)	37 ± 0.4 (36.40 – 37.80)	37 ± 0.5 (36.50 – 38.10)
Hemoglobin, *g/dl*	88.3 ± 9 (71-107)	87.2 ± 9.6 (73-112)	88.8 ± 9.8 (71-106)
Creatinine, *umol/l*			
≤ 110 umol/l	12 (40)	15 (50)	14 (46.7)
> 110 umol/l	18 (60)	15 (50)	14 (46.7)
Oxygen supply [a], *yes*	14 (46.7)	11 (36.7)	12 (40)
Positive fluid balance ≥ 2 liters [b], *yes*	14 (46.7)	12 (40)	11 (36.7)
Medication, *yes*			
Any psychotropic [c]	17 (56.7)	17 (56.7)	11 (36.7)
Any that could influence NIRS values [d]	12 (40)	11 (36.7)	10 (33.3)

[a] Presence of oxygen supply via nasal cannula or oxygen mask at the moment of oximetry assessment. [b] Positive liquid in/out balance of ≥ 2 liters in the 24 hours prior to oximetry assessment [c] Receiving a dose of any psychotropic medication within two hours prior to delirium assessment [d] Receiving a dose of any of the following medication within two hours prior to oximetry assessment using NIRS : antiarrhythmic, sympathomimetic, vasodilator or anti-hypertensive medication.

Table 5. Oximetry and delirium assessments.

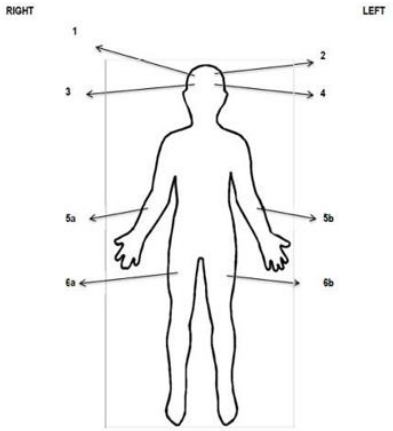
	***n* (%) or mean± standard deviation (min-max)**		
	Day 1 (n=30)	**Day 2 (n=30)**	**Day 3 (n=28)**
Oximetry related clinical data			
Cerebral oximetry [a]	50.8 ± 6.8 (30-64)	53.2 ± 6.9 (35-63)	54.3 ± 5.3 (45-64)
Peripheral oximetry [a]	67.1 ±4.8 (58-76)	67.8 ±4.7 (60-75)	67.5 ± 4 (61-77)
Delirium related clinical data			
ICDSC scores	4.6 ± 1.2 (1-7)	3.1 ± 2.2 (0-7)	2.3 [c] ± 2.4 (0-8)
DI scores	11.3 ± 3.8 (2-18)	6.6 ± 5.9 (0-20)	4.4 [c] ± 6 (0-18)
CAM-ICU positive scores	28 (93.3)	17 (56.7)	8 [c] (32)
Delirium diagnosis	28 (93.3)	17 (56.7)	8 [c] (32)
Delirium related manifestations [b], *yes*			
Hypoactive	14 (46.7)	9 (30)	4 [c] (16)
Hyperactive	14 (46.7)	8 (26.7)	4 [c] (16)

a Assessed using the INVOS 5100. [b] State of patient at the moment of delirium assessment, either presenting hypoactive symptoms of hyperactive symptoms defined as agitation. [c] n=25: two patients were discharged early and three patients were highly sedated on day 3 following delirium onset, therefore delirium assessment could not be performed.

Table 6. Results of Marginal Models and Linear Mixed Models (LMM).

PARAMETERS	B ± SE	p-value	Odd Ratio (OR)	95% CI
Marginal model **H1**: CAM-ICU and Cerebral Oximetry				
Intercept	20.96 ± 4.41	< 0.001		
Time	-1.59 ± 0.37	< 0.001	0.21	(0.098 ; 0.428)
Cerebral oximetry	-0.32 ± 0.07	< 0.001	0.73	(0.635 ; 0.838)
Marginal model **H2**: CAM-ICU and Peripheral Oximetry				
Intercept	10.18 ± 5.69			
Time	-1.40 ± 0.29	< 0.001	0.25	(0.139 ; 0.435)
Peripheral oximetry	0.01 ± 0.08	0.871	1.01	(0.872 ; 1.176)
Acute kidney injury	1.38 ± 0.68	0.041	3.97	(1.057 ; 14.905)
PARAMETERS	**B ± SE**	**p-value**		**95% CI**
LMM **H3**: Delirium Index and Cerebral Oximetry				
Intercept	48.76 ± 6.89			
Time	-2.76 ± 0.48	< 0.001		(-3.717 ± -1.804)
Cerebral oximetry	-0.43 ± 0.09	< 0.001		(-0.625 ± -0.242)
Hemoglobin	-0.15 ± 0.05	0.013		(-0.264 ; -0.031)
LMM **H4**: Delirium Index and Peripheral Oximetry				
Intercept	28.78 ± 9.96			
Time	-3.60 ± 0.49	< 0.001		(-4.594 ; -2.610)
Peripheral oximetry	-0.06 ± 0.12	0.595		(-0.322 ; 0.186)
Hemoglobin	-0.13 ± 0.06	0.037		(-0.256 ; -0.007)
Positive fluid balance of ≥2 liters during ICU stay, before delirium	3.89 ± 1.37	0.008		(1.078 ; 6.719)

Figure 1 – Oximetry measuring sites



Oximetry values were collected at six different sites on the body and these include all cerebral sites (1, 2, 3 and 4) in addition to one arm and one leg (5a and 6a OR 5b and 6b).