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Impact of Intraoperative Events on Cerebral Tissue Oximetry in Patients Undergoing Cardiopulmonary Bypass

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Abstract: Previous studies showed that decreased cerebral saturation during cardiac surgery is related to adverse postoperative outcome. Therefore, we investigated the influence of intraoperative events on cerebral tissue saturation in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). A total of 52 adult patients who underwent cardiac surgery using pulsatile CPB were included in this prospective explorative study. Cerebral tissue oxygen saturation ($SctO_2$) was measured in both the left and right cerebral hemisphere. Intraoperative events, involving interventions performed by anesthesiologist, surgeon, and clinical perfusionist, were documented. Simultaneously, in-line hemodynamic parameters (partial oxygen pressure, partial carbon dioxide pressure, hematocrit, arterial blood pressure, and CPB flow rates) were recorded. Cerebral tissue saturation was affected by anesthetic induction ($p < .001$), placement of the sternal retractor ($p < .001$), and initiation ($p < .001$) as well as termination of CPB ($p < .001$). Placement ($p < .001$) and removal of the aortic cross-clamp ($p = .026$ for left hemisphere, $p = .048$ for right hemisphere) led to changes in cerebral tissue saturation. In addition, when placing the aortic cross-clamp, hematocrit ($p < .001$) as well as arterial ($p = .007$) and venous ($p < .001$) partial oxygen pressures changed. Cerebral tissue oximetry effectively identifies changes related to surgical events or vulnerable periods during cardiac surgery. Future studies are needed to identify methods of mitigating periods of reduced cerebral saturation. **Keywords:** cardiopulmonary bypass, pulsatile flow, cerebral tissue oximetry, near-infrared spectroscopy. *JECT. 2015;47:32–37*

Despite impressive improvements in the overall safety of cardiac surgery, perioperative cerebral injury remains a major concern (1). The two major causative factors for neuropsychological dysfunction after cardiac surgery are global brain hypoperfusion and cerebral emboli generated by either surgical or perfusion-related interventions (2–6). Furthermore, worsened control of cerebral blood flow due to hypertension, diabetes, or other conditions imposes patients intraoperatively to increased risk of neurological complications (7,8). However, evaluation of cerebral hemodynamics may still not be part of routine practice (9).

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Intraoperative cerebral monitoring to identify vulnerable periods during cardiac surgery that require prompt intervention (e.g., adjusting the partial carbon dioxide gas pressure or fraction of inspired oxygen) should be a major goal in the fields of cardiac anesthesia, surgery, and perfusion (10,11). In a randomized, blinded, prospective study of 200 patients, Murkin et al. (12) demonstrated that non-invasive regional cerebral saturation monitoring is associated with a significant improvement in overall outcome after cardiac surgery.

Moreover, using a protocol-based interventional strategy to maintain cerebral saturation within 75% of baseline values during cardiopulmonary bypass (CPB) may improve both neurological and multi-organ dysfunction outcomes in cardiac surgery (12,13). Using the brain as an index organ for adequate tissue perfusion may therefore be beneficial for all vital organs (14). Routine monitoring of cerebral saturation during cardiac surgical interventions may therefore detect early signs of post-surgery neurological deficits.

In this study, intraoperative events were recorded to qualify the effects on cerebral tissue oxygen saturation ($SctO_2$) in patients undergoing cardiac surgery with pulsatile CPB.

MATERIALS AND METHODS

Patients

This prospective, explorative non-randomized clinical study included 52 adult patients (38 male and 14 female) that underwent elective cardiac surgery using pulsatile CPB between November 2011 and May 2012. No restrictions or inclusion criteria were applied. Institutional approval was received for this evaluation and since the study did not influence the routine care of the patient, informed consent was waived.

Non-invasive absolute $SctO_2$ was routinely measured via near-infrared spectroscopy (FORE-SIGHT; CAS Medical Systems, Inc., Branford, CT) by placing a fiber optic sensor on each side of the patient's forehead. Cerebral oximetry was measured in both the left and right hemisphere. $SctO_2$ data were simultaneously recorded every 2 seconds. All intraoperative events from anesthetic induction to discharge from the operating room were marked including the corresponding time in the data file. No interventions based on $SctO_2$ changes were applied intraoperatively and data used for analysis were routine measurements.

Anesthesia

After establishing standard anesthetic monitoring including electrocardiogram, oxygen saturation, and invasive arterial blood pressure (ABP) measurement, general anesthesia was induced with .5 μg/kg sufentanil, 1.5 mg/kg propofol, and .6 mg/kg rocuronium. After endotracheal intubation, the patients were ventilated with volume-controlled ventilation with tidal volumes of 7–8 mL/kg, positive end-expiratory pressure of 5 $cm \cdot H_2O$, respiratory rate of 12/min, and a fraction of inspired oxygen of .4, which resulted in normocapnia and normal oxygen saturation. Anesthesia was maintained with sevoflurane at a minimal alveolar concentration of approximately .8. Perioperative analgesic regime contained continuous intravenous administration of (*S*)-ketamine, lidocaine, and boluses of sufentanil.

Prior to surgery a warming blanket (3M Bair Hugger, 3M Health Care, Delft, The Netherlands) was positioned to maintain normothermia.

Cardiopulmonary Bypass

The CPB system included a standard hollow-fiber membrane oxygenator (Capiox SX18R; Terumo Medical Corp., Tokyo, Japan), a roller pump (S5; Sorin Group S.p. A, Mirandola, Italy), a cardiotomy reservoir (Capiox CXCRXA, Terumo), a collapsible venous reservoir (JVR 1900; Maquet Cardiopulmonary AG, Rastatt, Germany), and an arterial line filter (Leukogard-6; Pall, East Hills, NY). The standard priming of the CPB circuit consisted of 1500 mL of 4% gelofusin (B. Braun Melsungen AG, Melsungen, Germany), 200 mL of 20% mannitol (Viaflo; Baxter BV, Utrecht, The Netherlands), 100 mL of 20% human albumin (Albuman; Sanquin, Utrecht, The Netherlands), 50 mL of 8.4% $NaHCO_3$, and 20 mL of 10% calcium gluconate (B. Braun Melsungen AG). The total volume of the CPB priming amounted to 1870 mL clear fluid, containing 7500 IU heparin (Leo Pharmaceutical Products BV, Weesp, The Netherlands). The activated coagulation time was kept >400 seconds during bypass. Myocardial preservation was provided via the aortic root or selectively via the coronary ostia by a single dose of cardioplegic solution (800 ± 200 mL; St. Thomas' Hospital No. 1) at 4°C. Depending on the patients' body surface area, the ascending aorta was cannulated using either a 22- or 24-Fr cannula (Maquet Cardiopulmonary AG). A dual-stage venous cannula (32/40 or 36/51 Fr; Edwards Lifesciences BV, Breda, The Netherlands) was used for gravity drainage during coronary artery bypass grafting and aortic valve surgery. In case mitral or tricuspid valve surgery was involved, the venae cavae were cannulated separately using a DLP single-stage metal tip cannula (28 and 31 or 24 and 28 Fr; Medtronic, Inc., Minneapolis, MN).

Target flow rates of ≥2.6 $L/min/m^2$ body surface area were maintained throughout normothermic (36.3°C) CPB. Pulsatile flow (radial artery pulse pressure ≥25 mmHg) was used only during the period of cross-clamping with a frequency of 70 beats per minute, a base flow of 28% (1.4 L/min), and a pulse width of 50% (.42 seconds). Mean ABP was maintained at 80 ± 10 mmHg by titration of phenylephrine (.4 mg/mL) via an infusion pump if necessary. The sweep gas and fraction of inspired oxygen settings for the oxygenator were titrated to maintain normocapnia (arterial partial carbon dioxide pressure—$paCO_2$ 4.5–5.5 kPa) and normoxia (partial arterial oxygen pressure—paO_2 11.0–14.0 kPa). All patients received tranexamic acid (2 mg) during CPB. The transfusion trigger during CPB was set at a hematocrit level <25%. Pericardial blood was drained and washed with a cell saver device.

During valve and aortic root procedures, carbon dioxide flooding was routinely used. By maintaining in-line normocapnia, no episodes of high $paCO_2$ that could have potentially influenced the cerebral saturation occurred.

Near-Infrared Spectroscopy

Cerebral tissue oximetry is measured non-invasively as described by Murkin and Arango (14). In short, oxygen content in the frontal lobes is measured by near-infrared light penetrating the skin, skull, and other protective

tissues. Near-infrared light (660–940 nm) is partly scattered by chromophores within the tissue, absorbed by oxyhemoglobin or deoxyhemoglobin. The fiber optic sensors used in this study emit light at four different wavelengths to obtain greater precision for the estimation of oxygen content.

Data Processing

To be able to relate changes in cerebral saturation to occurring events, several hemodynamic parameters were recorded continuously during CPB: pump flow, ABP, as well as continuous in-line $paCO_2$ and paO_2, venous saturation, and electrolytes measurement via an optical fluorescence and reflectance-based system (CDI-500, Blood Parameter Monitoring System; Terumo, Japan). Pump flow was recorded by an ultrasonic flow monitor (Transonic Systems Europe BV, Maastricht, The Netherlands). All in-line measurements except for $SctO_2$ were collected using a data acquisition system (M-PAQ; Maastricht Instruments, Maastricht, The Netherlands). To combine all data, sample frequencies had to be equalized in all files. To achieve this, data were either averaged (decreasing the frequency of measuring), or the same data point was duplicated and added after its original data point (increasing the frequency of measuring). Subsequently, data synchronization was performed. For further data analysis, samples of 5 minutes were selected. One time sample was selected prior to the event, and the other one during the event.

Statistical Analysis

Data are shown as mean ± SD or as median (interquartile range), depending on data distribution. A p-value of <.05 was considered statistically significant.

For events occurring before or after CPB, only cerebral $SctO_2$ and ABP were compared between samples prior and during the event. For placement and removal of the aortic cross-clamp, cerebral $SctO_2$, mean ABP, pump flow, and blood parameters ($PaCO_2$, PaO_2, PvO_2, and hematocrit) were compared. If one or more parameters differed significantly between the two samples, a possible cause of the difference in $SctO_2$ could be determined.

Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL). Distribution of data was tested using the Shapiro–Wilk test. The paired student's t test or Wilcoxon signed-rank test was used to compare cerebral saturation measurement before and during events.

RESULTS

Demographic and baseline data for the 52 enrolled patients are listed in Table 1. Surgical- and perfusion-related data are presented in Table 2.

Table 1. Demographic and baseline data.

Gender (male/female)	38/14
Age (years)	*68 (59.3–75.8)*
BMI (kg/m^2)	*26.0 (24.4–27.8)*
Diabetes mellitus (yes/no)	7/45
Peripheral vascular disease (yes/no)	4/48
Mean ABP pre-CPB (mmHg)	102.1 ± 11.3
$SctO_2$ mean pre-CPB (%)	*70 (66–71)*
Mean Hct pre-CPB (%)	41.0 ± 3.9

ABP, arterial blood pressure; BMI, body mass index; CPB, cardiopulmonary bypass; Hct, hematocrit; $SctO_2$, cerebral tissue oxygen saturation.
Parameters in italics are shown as median (interquartile range), and remaining parameters are shown as absolute numbers or mean ± SD.

Table 2. Surgical and perfusion data.

Isolated CABG surgery	59.7% (n = 31)
Isolated valve surgery	23.1% (n = 12)
CABG + valve surgery	13.5% (n = 7)
Ascending aorta replacement	3.8% (n = 2)
CPB time (minutes)	*80 (69–105)*
Aortic cross-clamp time (minutes)	*55 (43–70)*
Mean Hct (%) during CPB	*28 (25–29)*
Mean pump flow (L/min)	4.3 ± 0.5
Mean ABP (mmHg) during CPB	*75 (71–80)*

ABP, arterial blood pressure; CABG, coronary artery bypass grafting; Hct, hematocrit.
Data for mean pump flow is presented as mean ± SD. Data for CPB time, aortic cross-clamp time, Hct and ABP are presented as median (interquartile range).

During the entire intraoperative period, cerebral $SctO_2$ showed comparable values for both left and right hemisphere. Left and right mean $SctO_2$ values of 71 ± 4% and 70 ± 4% were found prior to CPB, 66 ± 4% and 65 ± 4% during CPB, and 70 ± 4% and 69 ± 5% after CPB, respectively. Since the difference between the left and right hemisphere can be neglected, the influence of intraoperative events on $SctO_2$ are depicted in Figure 1 using mean values.

Onset of CPB, placement and removal of the aortic cross-clamp (difference in significance between hemispheres, p = .026 for the left and p = .048 for right hemisphere) resulted in a decrease in $SctO_2$, whereas anesthetic induction (p < .001), placement of the sternal retractor (p < .001), and termination of CPB (p < .001) showed to be related to an increase in $SctO_2$ (Figure 1). Furthermore, phenylephrine infusion (p = .356), hemofiltration (p = .892), and removal of the sternal retractor (p = .692 for the left hemisphere, p = .123 for the right hemisphere) did not result in a significant $SctO_2$ change. Aortic cross-clamping showed to have a statistically significant impact on cerebral saturation as shown in Figure 1, which may in part be explained by differences in arterial and venous blood gas parameters and hematocrit. During placement of the aortic cross-clamp, hematocrit decreased significantly (p < .001), as well as arterial (p = .007) and venous

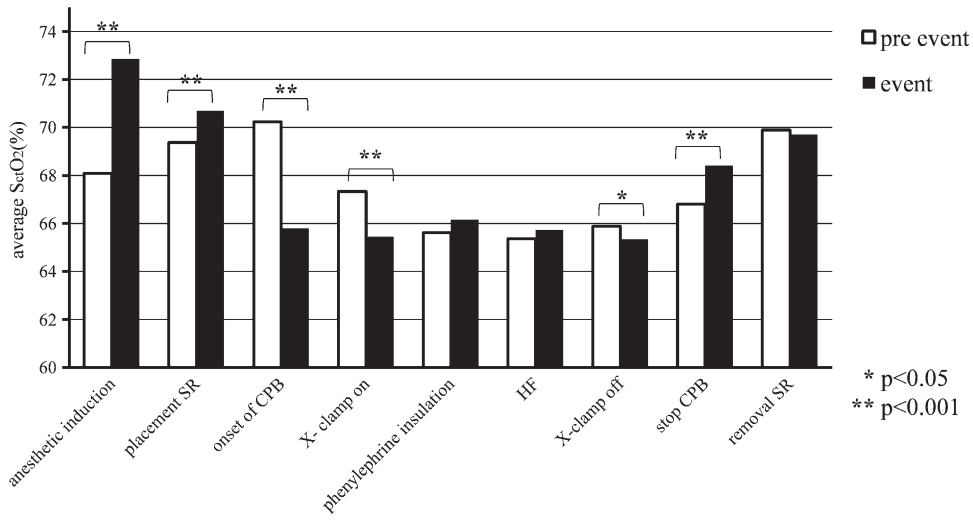

Figure 1. Influence of intraoperative events on mean cerebral $SctO_2$. CPB, cardiopulmonary bypass; HF, hemofiltration; $SctO_2$, cerebral oxygenation; SR, sternal retractor; X-clamp, aortic cross-clamp.

($p < .001$) oxygen levels (Table 3). The changes in hematocrit, arterial, and venous pO_2 did not occur during removal of the aortic cross-clamp.

In all cases, the postoperative period was uneventful and no intraoperative cerebral ischemic episode occurred.

DISCUSSION

Intraoperative events showed to affect cerebral oximetry in patients undergoing cardiac surgery with CPB. Since previous studies suggest that a fall in cerebral saturation is related to adverse neurological outcome, routine measurement of cerebral saturation warrants early detection of brain ischemia during surgery (12–14).

Our results showed subtle changes in $SctO_2$ readings following several events that appeared statistically significant while absolute differences were relatively small and far from the suggested 20% decrease when intervention is required (14). Presumably the events did not provoke any therapeutically relevant changes in cerebral tissue saturation in our study. One can speculate that maintaining normocapnia, normoxia, and a tight blood pressure control led to minimized fluctuations in cerebral saturation. Iatrogenic events, i.e., placement of the aortic cross-clamp can still induce changes in cerebral saturation, which do not necessarily require intervention. On the other hand, the extent of cerebral desaturation requiring an intervention may vary between different sensors, implying that no fixed thresholds have been set (15). Nonetheless, cerebral oximetry enables clinicians to observe slight changes in cerebral saturation, which may help to prevent further desaturations.

Induction of general anesthesia resulted in a steep increase in cerebral $SctO_2$, which may be explained by pre-oxygenation with a high-inspired fraction of oxygen

Table 3. Influence of aortic cross-clamping on hemodynamic parameters.

Aortic cross-clamp on		Prior to cross-clamping	During cross-clamping	*p*-Value
	Mean ABP (mmHg)	*72.4 (63.4–80.3)*	*73.9 (63.5–79.2)*	.420
	$paCO_2$ (kPa)	*5.5 (5.1–5.6)*	*5.4 (5.0–5.6)*	.792
	paO_2 (kPa)	*14.9 (12.6–18.0)*	*13.0 (12.3–16.5)*	.007
	pvO_2 (kPa)	5.9 ± 1.0	5.3 ± .6	<.001
	Hct (%)	*28.7 (26.5–31.6)*	*26.4 (24.6–29.0)*	<.001
	CPB flow (L/min)	*4.3 (3.8–4.7)*	*4.4 (4.0–4.7)*	.680
Aortic cross-clamp off		Prior to cross-clamp removal	After cross-clamp removal	*p*-Value
	Mean ABP (mmHg)	*74.4 (68.7–80.7)*	*71.6 (67.2–77.7)*	.196
	$paCO_2$ (kPa)	*5.5 (5.2–5.7)*	*5.5 (5.3–5.7)*	.017
	paO_2 (kPa)	14.0 ± 2.9	14.4 ± 2.7	.255
	pvO_2 (kPa)	5.1 ± .5	5.1 ± .6	.535
	Hct (%)	*27.4 (24.0–29.0)*	*27.5 (23.7–29.6)*	.761
	CPB flow (L/min)	*4.1 (2.0–4.7)*	*3.7 (.1–4.6)*	.093

ABP, arterial blood pressure; CPB, cardiopulmonary bypass; Hct, hematocrit; $paCO_2$, arterial carbon dioxide level; paO_2, arterial oxygen level; pvO_2, venous oxygen level.

and unchanged cardiac output (16). Conversely, a significant decrease in mean $SctO_2$ occurred with onset of CPB, which can presumably be explained by acute hemodilution, as the hematocrit dropped from approximately 41% to 28% (Tables 1 and 2). These findings are in line with the study of Han et al. (17) who showed that acute normovolemic hemodilution is associated with a fall in cerebral saturation. Rapid initiation of CPB mostly provoked a drop in $SctO_2$ as resultant of assanguinous priming solution passage through the cerebral vasculature with inadequate oxygen delivery to the brain.

Placement of the sternal retractor is another factor influencing the cerebral saturation as measured by near-infrared spectroscopy. One could hypothesize that the change in cerebral saturation is caused by strong pain signals transported via the spinal cord during the event. In theory, this causes an immediate elevation in ABP. However, this effect is not observed in this study, which is potentially due to adequate anesthesia and analgesia. Another theory is that opening the thoracic cavity influenced intrathoracic pressures and venous return, resulting in an increased cerebral saturation. On the other hand, removal of the sternal retractor did not show a significant difference in $SctO_2$. A plausible explanation for this observation is that the hypothesized pain signals were not activated or not in an extent large enough to cause a significant difference. Also, instead of generating pressure on the site of the sternum and surrounding tissue (as in placement of the sternal retractor), the opposite effect could have taken place, i.e., relaxation.

Another event that showed to affect cerebral saturation is aortic cross-clamping, which may in part be explained by differences in arterial and venous blood gas parameters and hematocrit (Table 3). Placement of the aortic cross-clamp resulted in sudden excessive withdrawal of blood volume from patient to the heart–lung machine by lowering the CPB flow. This resulted in loss of cardiac output and a drop in ABP with concomitant negative consequences on oxygen delivery to the brain, as reflected by significantly lowered values of pO_2 in both arterial and venous blood. CPB flow was not significantly different between samples of placement and removal of the cross-clamp, most likely because the duration of lowered flow was too short and the heart–lung machine was at optimal flow before and after both these events. In contrast, the decrease in arterial and venous pO_2 did not appear while removing the cross-clamp as by routine during removal of the aortic cross-clamp the CPB flow and ABP are not actively lowered.

Vasoconstriction using phenylephrine infusion did not appear to affect cerebral saturation, which is in contrast with the results of a previous study by Moerman et al. (18). However, Brassard et al. (19) recently showed that the negative effect might only be present in diabetic patients.

Finally, a study limitation is the lack of an intervention-guided design. Physiologic parameters are kept within a certain range, preventing major fluctuations in cerebral tissue saturation during the intraoperative period. Furthermore, data synchronization involving the equalization of the sample frequency led to data (pump flow and ABP) to be leveled out and small fluctuations to be diminished compared to the raw data.

In conclusion, cerebral tissue oximetry by near-infrared spectroscopy effectively identifies subtle changes in cerebral saturation related to surgical events or vulnerable periods during cardiac surgery. Future studies in larger cohorts are required to identify therapeutically relevant changes in cerebral saturation as measured by cerebral oximetry.

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