Effect of changes in cerebral oximeter values during cardiac surgery on the incidence of postoperative neurocognitive deficits (POND): A retrospective study based on propensity score–matched analysis

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Abstract

Objectives
The occurrence of postoperative neurocognitive deficits (POND) after major cardiac surgery is associated with an increase in perioperative mortality and morbidity. Oxidative stress caused by oxygen can affect neuronal damage, which can lead to POND. Whether the intraoperative rSO2 value reflects oxidative stress and the associated incidence of POND is unknown.

Methods
Among 3482 patients undergoing cardiac surgery, 976 patients were allocated for this retrospective study. Of these, 230 patients (32.5%) were observed to have postoperative neurologic symptoms. After propensity score 1:2 ratio matching, a total of 690 patients were included in the analysis. Recorded data on the occurrence of POND from the postoperative period to predischarge were collected from the electronic records.

Results
The mean baseline rSO2 value was higher in the POND (−) group than in the POND (+) group. The mean overall minimum rSO2 value was lower in the POND (+) group (52.2 ± 8.3 vs 48.3 ± 10.5, \(P < 0.001\)). The mean overall maximum rSO2 values were not significantly different between the two groups (72.7 ± 8.3 vs 73.2 ± 9.2, \(P = 0.526\)). However, there was a greater increase in the overall maximum rSO2 values as compared with baseline in the POND (+) group (10.9 ± 8.2 vs 17.9 ± 10.2, \(P < 0.001\)). The degree of increase in the maximum rSO2 value was a risk factor affecting the occurrence of POND (adjusted odds ratio, 1.6).
1.08; 95% confidence interval [CI], 1.04–1.11; P < 0.001). The areas under the receiver-operating characteristic curve for delta values of minimal and maximal compared with baseline values were 0.60 and 0.71, respectively.

**Conclusions**

Increased cerebral oximeter levels during cardiac surgery may also be a risk factor for POND. This is considered to reflect the possibility of oxidative neuronal damage, and further studies are needed in the future.

**Introduction**

The incidence of postoperative neurocognitive deficits (POND) after major cardiac surgery ranges from 25% to 80% [1,2]. Alterations in systemic and regional perfusion and oxygenation, exposure to anesthetic agents, cardiopulmonary bypass (CPB), and rapid changes in plasma pH and cellular metabolism during cardiac surgery induce oxidative stress that can contribute to postoperative delirium [3–5]. POND is associated with an increase in perioperative mortality and morbidity, longer hospital stay, and a prolonged rehabilitation process. Regional cerebral oxygen saturation (rSO2) is monitored using near-infrared spectroscopy (NIRS) during cardiac surgery to detect reduced oxygen supply to the brain [6,7].

The cerebral oximeter is widely used to detect changes in cerebral oxygen saturation and cerebral ischemia during cardiac surgery [8]. Previous studies have demonstrated that when brain oxygen saturation levels are reduced by more than 30% relative to baseline during cardiac surgery, a correlation is observed between POND, intensive care unit, and increased length of hospital stay [8–11]. However, these previous studies focused on the occurrence of neurocognitive deficits after surgeries in which the cerebral oximeter values decreased, and recent studies have focused on and proven that oxidative stress caused by oxygen can affect neuronal damage [4,5]. Lopez et al reported that oxidative damage is associated with occurrence of POND as a result of direct neuronal damage as well as destruction of the blood–brain barrier [12].

We hypothesized that not only the degree of decrease in rSO2 value but also the degree of increase in rSO2 value could affect the occurrence of POND. Therefore, we retrospectively investigated the association between the incidence of POND and intraoperative values of rSO2 in cardiac surgery.

**Method**

**Patients**

This retrospective study was approved by the institutional review board (IRB) of Samsung Medical Centre (approval No. 2019-02-083, March 5, 2019). Because of the retrospective nature of the study, in which the medical records of patients who had already undergone the operation were analyzed, the IRB waived the requirements for informed consent. The inclusion criterion was adult patients aged 20 years or older who underwent cardiac surgery on CPB between January 2015 and December 2018. For patients who underwent two or more surgeries, we included only the final surgery in the analysis. Exclusion criteria were pediatric patients, patients without a CPB period, and patients with missing data during surgery.
Anesthesia and CPB

Anesthesia was induced, and total intravenous anesthesia was maintained with remifentanil, propofol, and rocuronium via peripheral line during the operation. The anesthetic agent was titrated for a bispectral index between 40 and 60. The maintenance fluid was crystalloid solution, infused at a rate of 5 mL·kg⁻¹·h⁻¹. Hemoglobin level was maintained at ≥ 9g/dL [13]. The rates of fluid administration and red blood cell transfusion were adjusted in consideration of estimated blood loss according to our institution’s protocol. Mechanical ventilation was controlled to maintain normocarbia (PaCO₂ 4.7–5.0 kPa) throughout surgery, except during CPB, when a continuous positive airway pressure of 5 cmH₂O with 50% oxygen was applied. Vasoactive drugs (dopamine, dobutamine, nitroglycerin, norepinephrine, milrinone, and epinephrine) were administered to maintain hemodynamic stability throughout the operation period. CPB was performed using bivacal cannulation with mild hypothermia. For myocardial protection, both intermittent cold blood cardioplegia via the antegrade or retrograde route and topical cooling with ice slush were used. In patients with significant aortic regurgitation, retrograde cardioplegia was infused using direct coronary sinus cannulation. PaCO₂ and pH were managed during the CPB period in accordance with the a-stat strategy.

Regional cerebral oximetry monitoring

Regional cerebral oximetry was obtained with NIRS monitoring performed using sensors placed bilaterally on the patient’s forehead during cardiac surgery (sensor and monitor: Medtronic/Covidien INVOS cerebral/somatic oximetry adult sensors, Somanetics Corporation, Troy, MI, USA). The baseline rSO₂ value was obtained while the patient was breathing room air, and subsequent rSO₂ values were recorded at 5-minute intervals throughout the duration of the surgical period, beginning 1 minute after the sensor was placed.

Propensity score matching

All patients were divided according to the presence or absence of postoperative neurologic symptoms. To compensate for demographic imbalance, we performed propensity score matching between the two groups. This method consisted of determining cases and controls and then selecting the first case and finding the control with the closest propensity score. A logistic regression model was built given the covariates of age, sex, body mass index, presence of cerebrovascular accident history, type of operation, and comorbidities (e.g., diabetes mellitus, hypertension, arterial fibrillation, and myocardial infarction). We applied 1:2 nearest-neighbor matching without replacement to ensure that conditional bias was minimized. Propensity score matching was performed using the Matchit package R (R Foundation for Statistical Computing).

Assessment of neurologic problem and data acquisition.

We collected recorded data on the new development of POND from the postoperative period to predischarge from the electronic records. Diagnosed POND categorized as stroke, intracranial hemorrhage, delirium, seizure and coma. Unspecified PONDs and behaviors include cases such as agitation, confusion and delayed mental recovery, which were recorded in the electronic medical record but not registered as a diagnosis. [14,15] Delirium assessment was performed using the confusion assessment method for the intensive care unit (CAM-ICU) [16]. When patients were discharged from the ICU, we assessed delirium using the confusion assessment method (CAM). Delirium, as defined by the CAM, was classified and categorized into four categories: acute onset of changes or fluctuations in the course of mental status, inattention, disorganized thinking, and altered level of consciousness. The CAM-ICU measures the acute onset of fluctuation of mental status changes, and patients were followed up daily with the Glasgow Coma
Scale and an agitation/sedation scale (Richmond Agitation Sedation Scale; supplementary file) [17,18]. The CAM-ICU and CAM testers were assessed and recorded by individuals who received training and had been performing these tests for a number of years. Patients were assessed for delirium at least once daily until discharge, and the results were recorded in the electronic medical record. The primary outcome is the comparison of the predicted degree of POND occurrence according to the change in rSO₂ value. The secondary outcome is the effect of changes at each stage of surgery on the occurrence of POND as compared with the baseline.

**Statistical analysis**

We performed 1:2 propensity score matching, which is a method used to reduce confounding effects in observational studies [19]. Continuous variables were compared using the t test or Mann–Whitney U test as appropriate. Categorical variables were analyzed using Pearson’s chi-square test or Fisher’s exact test as appropriate. Data are presented as means (standard deviations). We performed logistic regression analysis to obtain the crude odds ratio and adjusted odds ratio of the values for each operation period’s rSO₂ on POND. A receiver-operating characteristic (ROC) curve was constructed using cerebral oximeter values, and we calculated the area under the ROC (AUROC) to assess the prediction of POND. Cutoff values were set using the maximum of the Youden index (J). The Delong test was used to compare the AUROC between ROC curves. Statistical analyses were performed using SPSS version 22 (SPSS Inc.), R statistical software version 3.5.3 (Vienna, Austria; https://www.r-project.org/), and Medcalc software (Ostend, Belgium). A P value less than 0.05 was considered statistically significant.

**Results**

We assessed the study eligibility of 3482 patients (Fig 1). Of these, 2506 patients were excluded for the following reasons: (1) 1021 patients were pediatric patients, (2) 515 patients underwent cardiac surgery without CPB, and (3) 970 patients were excluded due to a lack of intraoperative cerebral oximeter data. Therefore, 976 patients were allocated for this retrospective study. Among these, 230 patients (32.5%) were observed to have postoperative neurologic symptoms. After propensity score 1:2 ratio matching, a total of 690 patients were included in the final analysis (Fig 1).

Table 1 shows the patient characteristics. Table 2 shows the rSO₂ values for each operation period. In raw rSO₂ values, baseline and overall minimum values showed significant differences between the two groups (P<0.001, respectively). The baseline rSO₂ value was lower in the POND (+) group than in the POND (-) group (61.9 ± 9.6 vs 55.3 ± 11.4; P < 0.001). The mean overall minimum rSO₂ value was lower in the POND (+) group (52.2 ± 8.3 vs 48.3 ± 10.5, P < 0.001). There were significant differences between the two groups in changes of preweaning, postweaning, overall minimum, and overall maximum values compared to baseline (Δ). In the POND (+) group, there was a significant increase in rSO₂ values in the pre- and post-CPB weaning periods. (Δ(baseline–preweaning), 2.0 ± 10.1 vs 9.2 ± 13.1, P < 0.001; Δ(baseline–postweaning), 7.1 ± 9.6 vs 13.1 ± 11.4, P < 0.001). As compared with baseline, there was a lesser decrease in the overall minimum rSO₂ values in the POND (+) group (−9.8 ± 7.7 vs −7.1 ± 8.7, P < 0.001). Overall maximal rSO₂ values were greater increased compared to baseline in the POND(+) group (10.9 ± 8.2 vs 17.9 ± 10.2, P < 0.001).

Table 3 shows the results of the multivariate logistic regression analysis on the variables that were significant in Table 2. The increase in the maximum rSO₂ value compared to the baseline was a risk factor affecting the occurrence of POND (adjusted odds ratio, 1.08; 95% confidence interval [CI], 1.04–1.11; P < 0.001).
Table 4 presents the perioperative variables. Duration of CPB, duration of aortic cross-clamp, anesthesia time, operation time, ventilation time, and mental recovery time were prolonged in the POND (+) group. Major organ mortality and morbidity were more frequent in the POND (+) group with new stroke, acute kidney injury, prolonged ventilation and death.

Fig 2 shows the ROC curve of intraoperative variables. The AUROC for delta values of minimal compared with baseline values (Δmin) was 0.60 (95% CI, 0.57–0.64). The AUROC for the delta values of maximal compared with baseline values (ΔMAX) was 0.71 (95% CI, 0.67–0.74). The delta values of maximal compared with baseline values were significantly more predictive of POND than the delta values of minimal compared with baseline values (P < 0.0001). The cut-off value of the delta maximal value was 15.5, and the sensitivity and specificity were 60% (95% CI, 53%–66%) and 75% (95% CI, 71%–79%), respectively. The cutoff value of the delta minimal value was −5, and the sensitivity and specificity were 44% (95% CI, 38%–52%) and 73% (95% CI, 68%–77%), respectively. The AUROC for intraoperative data CPB duration, ACC duration, anesthesia time, operation time, were 0.62 (0.58–0.65), 0.60 (0.57–0.64), 0.63 (0.60–0.67) and 0.62 (0.57–0.66), respectively. There was no statistically significant difference of AUROC between CPB duration, ACC duration, anesthesia time, operation time and Δmin. (P > 0.05)

Discussion
This retrospective study found that increased rSO2 values during operation may predict the development of POND. To the best of our knowledge, this is the first study to confirm retrospectively that not only a decrease in rSO2 but also an increase in rSO2 may affect the
The mechanism underlying the occurrence of POND in cardiac surgery remains unclear. Most previous studies focused on the desaturation event on rSO$_2$, which could adversely affect the incidence of POND and other postoperative outcomes. It is known that when the cerebral oximetry value decreases by more than 30% as compared with baseline, it is defined as cerebral desaturation [10]. Among patients aged 70 years or older who underwent coronary artery bypass graft surgery, those with a reduction of $\geq 50\%$ compared with baseline rSO$_2$ had a high incidence of early-onset POND, and those with a reduction of $\geq 30\%$ compared with baseline rSO$_2$ had a high incidence of late-onset POND [20]. In contrast, the findings of a recent prospective randomized trial reported no difference between intraoperative rSO$_2$ values and POND after cardiac surgery [21]. That is, the decrease in rSO$_2$ was not absolutely predictive of POND. The research trend on the relationship between rSO$_2$ and the occurrence of POND has been changing.

Meanwhile, there is no controversy about the possibility of organ injury after the transition from the ischemic state to hyperoxic reperfusion during surgery [22]. There is a possibility of hyperoxic damage to brain tissue during reperfusion and during oxygenation after the transition from CPB to spontaneous circulation during cardiac surgery [23]. Hyperoxic reperfusion-induced vasoconstriction or oxidative injury are mechanisms for the association between hyperoxic cerebral reperfusion and POND [24,25]. During hyperoxic reperfusion, there is an increase in oxidative neuronal damage, and F2-isoprostanes and isofurans increase in plasma as markers of systemic oxidative neuronal damage [26,27]. F2-isoprostanes are associated with brain arteriole vasoconstriction, and isofurans have been found to be mediators between hyperoxia and POND [28,29]. In addition to F2-isoprostanes and isofuran, S100 calcium-

| Table 1. Baseline patient characteristics. | Postoperative neurologic symptom (-) (n = 460) | Postoperative neurologic symptom (+) (n = 230) | P value |
|------------------------------------------|-----------------|-----------------|---------|
| Gender (female/male)                     | 224/236         | 111/119         | 0.979   |
| Age, years                               | $62.0 \pm 14.6$ | $62.6 \pm 13.7$ | 0.568   |
| Weight, kg                               | $60.2 \pm 11.9$ | $60.9 \pm 11.8$ | 0.473   |
| Height, cm                               | $161.2 \pm 10.4$ | $162.7 \pm 10.0$ | 0.074   |
| BMI                                      | $23.1 \pm 3.4$  | $23.0 \pm 3.6$  | 0.736   |
| CVA history, n (%)                       | 106 (23)        | 70 (30)         | 0.045   |
| Type of surgery, n (%)                   |                 |                 |         |
| Valve                                    | 205(45)         | 108(47)         | 0.772   |
| Aorta                                    | 125(27)         | 62(27)          |         |
| CABG                                     | 4(1)            | 2(1)            |         |
| Others*                                   | 126(27)         | 58(25)          |         |
| Baseline ABGA                            |                 |                 |         |
| FiO$_2$                                   | $0.6 \pm 2.3$   | $0.5 \pm 0.2$   | 0.345   |
| PaCO$_2$                                 | $35.9 \pm 7.4$  | $35.2 \pm 4.7$  | 0.176   |
| PaO$_2$                                  | $191.0 \pm 87.2$ | $196.0 \pm 98.4$ | 0.515   |
| Glucose                                  | $116.7 \pm 37.3$ | $117.6 \pm 36.7$ | 0.775   |
| Baseline MAP                             | $72.1 \pm 15.2$ | $70.6 \pm 13.7$ | 0.189   |
| Baseline CVP                             | $7.1 \pm 9.8$   | $8.2 \pm 6.6$   | 0.080   |

BMI, body mass index; CVA, cerebrovascular accident; CVP, central venous pressure; MAP, mean arterial pressure; CABG, coronary artery bypass grafting.

* Type of others surgery included septal myectomy, VSD/ASD closure and cardiac mass removal.

Data are presented as the number of patients with percentage (%) or the mean ± SD.

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occurrence of POND. The use of cerebral oximeter is essential to predict the development of POND during major cardiac surgery.
binding protein B, an indicator of disruption to the blood–brain barrier by oxidative injury, was also higher in the POND group during cardiac surgery [5]. That is, the possibility that the blood–brain barrier can be destroyed by systemic oxidative damage during surgery and cause POND by neuronal injury was proven.

On the other hand, the association between the occurrence of POND and an increase in rSO\textsubscript{2} cannot be ruled out due to cerebral bleeding. CPB reduces platelet counts by about 50% and causes platelet dysfunction as well as reduced levels of clotting factors and von Willebrand factors [30,31]. A large volume of heparin is administered during CPB, and in the CPB-weaning process, it reverses to protamine. This process may have a rebound effect of

Table 2. rSO\textsubscript{2} values during the operation period.

| rSO\textsubscript{2} value | Postoperative neurologic symptom (–) (n = 460) | Postoperative neurologic symptom (+) (n = 230) | P value |
|---------------------------|---------------------------------------------|-------------------------------------------------|---------|
| **Baseline**              |                                             |                                                 |         |
| Right                     | 62.0 ± 10.2                                 | 54.8 ± 11.9                                     | <0.001  |
| Left                      | 61.7 ± 9.8                                  | 55.7 ± 11.5                                     | <0.001  |
| Mean                      | 61.9 ± 9.6                                  | 55.3 ± 11.4                                     | <0.001  |
| **Preweaning period**     |                                             |                                                 |         |
| Right                     | 64.0 ± 10.4                                 | 64.4 ± 12.2                                     | 0.674   |
| Left                      | 63.8 ± 10.0                                 | 64.6 ± 11.8                                     | 0.356   |
| Mean                      | 63.98 ± 9.8                                 | 64.58 ± 11.4                                    | 0.484   |
| Δ(baseline–preweaning)    |                                             |                                                 |         |
| Right                     | 2.0 ± 10.6                                  | 9.5 ± 13.7                                      | <0.001  |
| Left                      | 2.1 ± 10.4                                  | 8.9 ± 13.5                                      | <0.001  |
| Mean                      | 2.0 ± 10.1                                  | 9.2 ± 13.1                                      | <0.001  |
| **Postweaning period**    |                                             |                                                 |         |
| Right                     | 68.9 ± 6.5                                  | 68.0 ± 11.0                                     | 0.279   |
| Left                      | 68.8 ± 9.5                                  | 68.6 ± 11.1                                     | 0.805   |
| Mean                      | 68.98 ± 9.0                                 | 68.38 ± 10.3                                    | 0.478   |
| Δ(baseline–postweaning)   |                                             |                                                 |         |
| Right                     | 6.9 ± 9.9                                   | 13.2 ± 11.7                                     | <0.001  |
| Left                      | 7.1 ± 10.0                                  | 12.9 ± 12.2                                     | <0.001  |
| Mean                      | 7.1 ± 9.6                                   | 13.1 ± 11.4                                     | <0.001  |
| **Overall minimum**       |                                             |                                                 |         |
| Right                     | 52.1 ± 8.7                                  | 47.8 ± 11.5                                     | <0.001  |
| Left                      | 52.1 ± 9.0                                  | 48.8 ± 10.4                                     | <0.001  |
| Mean                      | 52.2 ± 8.3                                  | 48.3 ± 10.5                                     | <0.001  |
| Δ(baseline–minimum)       |                                             |                                                 |         |
| Right                     | −10.0 ± 8.4                                 | −7.1 ± 9.4                                      | <0.001  |
| Left                      | −9.4 ± 8.1                                  | −6.9 ± 8.7                                      | <0.001  |
| Mean                      | −9.8 ± 7.7                                  | −7.1 ± 8.7                                      | <0.001  |
| **Overall maximum**       |                                             |                                                 |         |
| Right                     | 73.0 ± 8.9                                  | 72.8 ± 9.8                                      | 0.828   |
| Left                      | 72.5 ± 8.6                                  | 73.6 ± 9.7                                      | 0.156   |
| Mean                      | 72.7 ± 8.3                                  | 73.2 ± 9.2                                      | 0.526   |
| Δ(baseline–maximum)       |                                             |                                                 |         |
| Right                     | 11.0 ± 8.5                                  | 18.0 ± 10.6                                     | <0.001  |
| Left                      | 10.8 ± 8.8                                  | 17.8 ± 10.7                                     | <0.001  |
| Mean                      | 10.9 ± 8.2                                  | 17.9 ± 10.2                                     | <0.001  |

Data are presented as the mean ± SD.

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heparin, which causes bleeding after CPB weaning. In a study of pediatric patients to detect intracerebral hemorrhage (ICH) using NIRS, 21 patients showed a ≥45% increase in NIRS value, 12 patients of whom had an actual ICH (sensitivity = 100%, specificity = 80%) [32]. When acute hemorrhage occurs, hemoglobin aggregation temporarily increases the cerebral oximeter level. In our study, we observed ICH in nine patients, and the maximal cerebral oximeter value increased by an average of 47% as compared with baseline. The rapid increase in rSO\textsubscript{2} during conversion from CPB to spontaneous flow also indicates that the possibility of ICH cannot be excluded. However, an increase in the cerebral oximeter value is not an absolute marker of ICH during cardiac surgery, because of the effects of anesthesia, ventilator, CPB flow, and so forth. Thus, there is a need for further prospective studies in the future.

Unfortunately, there is no gold standard to establish the diagnosis of POND. Therefore, the incidence of POND/POCD is dependent on definitions based on in each study. We applied the concept of postoperative neurocognitive deficits (POND), which combines the concepts of postoperative cognitive dysfunction (POCD) and postoperative delirium (POD). In a retrospective study, there is a limit to clearly distinguishing POCD from POD only with electronic

### Table 3. Logistic regression analysis.

|                | Crude OR (95%CI) | Crude \( P \) value | Adjusted OR (95%CI) | Adjusted \( P \) value |
|----------------|------------------|----------------------|----------------------|------------------------|
| Baseline       | 0.94 (0.92, 0.96)| <0.001               | 0.99 (0.96, 1.02)    | 0.415                  |
| Δ(baseline–postweaning) | 1.05 (1.04, 1.07)| <0.001               | 1.02 (0.99, 1.04)    | 0.141                  |
| Δ(baseline–postweaning) | 1.05 (1.03, 1.07)| <0.001               | 0.98 (0.95, 1)       | 0.084                  |
| Overall minimum| 0.95 (0.94, 0.97)| <0.001               | 0.98 (0.96, 1.01)    | 0.164                  |
| Δ(baseline–minimum) | 1.04 (1.02, 1.07)| <0.001               | 0.98 (0.96, 1.01)    | 0.175                  |
| Δ(baseline–maximum) | 1.09 (1.07, 1.11)| <0.001               | 1.08 (1.04, 1.11)    | <0.001                |

Data are presented as the mean (95% confidence interval).

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### Table 4. Other variables.

|                | POND (–) (\( n = 460 \)) | POND (+) (\( n = 230 \)) | \( P \) value |
|----------------|---------------------------|---------------------------|--------------|
| \( ^a \)CPB duration, min | 148.1 ± 63.3              | 181.1 ± 85.0              | <0.001       |
| \( ^a \)ACC duration, min    | 112.0 ± 54.4              | 135.2 ± 68.2              | <0.001       |
| \( ^a \)Anesthesia time, min | 390.3 ± 104.0             | 448.4 ± 140.9             | <0.001       |
| \( ^a \)Operation time, min  | 318.2 ± 102.7             | 368.9 ± 140.0             | <0.001       |
| \( ^b \)Ventilation time, min| 639.4 ± 1464.7            | 2278.0 ± 6428.0           | <0.001       |
| \( ^b \)Mental recovery, min | 335.4 ± 1458.9            | 1518.8 ± 6437.6           | 0.006        |
| \( ^b \)ICU stay, h         | 48.6 ± 96.9               | 109.1 ± 359.5             | 0.013        |
| \( ^3 \)MOMM                |                           |                           |              |
| New stroke (%)              | 0(0.0)                    | 36(15.7)                  | <0.001       |
| AKI (%)                     | 53(11.5)                  | 57(24.8)                  | <0.001       |
| Prolonged ventilation (%)   | 15(3.3)                   | 48(20.9)                  | <0.001       |
| Deep sternal infection (%)  | 9(2.0)                    | 7(3.0)                    | 0.531        |
| Reoperation (%)             | 15(3.3)                   | 12(5.2)                   | 0.298        |
| Death (%)                   | 4(0.9)                    | 22(9.6)                   | <0.001       |

Data are presented as the mean ± SD and percentage (%). ICU, intensive care unit; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; MOMM, major organ mortality; AKI, acute kidney injury.

\( ^a \)CPB duration time, ACC duration time, Anesthesia time and Operation time are intraoperative data

\( ^b \)Ventilation time, Mental recovery time, ICU stay and MOMM are postoperative data.

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medical records. In addition, previous studies demonstrated that POD and POCD occasionally occur in the same individual with overlapping risk factors have suggested a common underlying neuropathogenesis [15,33].

There are several limitations to our study. First, Study results may be affect confounding factors such as postoperative anxiety, pain and medications. The occurrence of POND/POCD is strongly dependent on expert opinion. Therefore, there is a possibility of false positives if the observer does not distinguish the confounding factors. Second, we cannot confirm the specific time point exactly. Most of the preweaning periods and postweaning periods in which most cerebral oximeter values were increased during surgery had maximal cerebral oximeter values, but the exact time point could not be determined. Third, we did not measure the O2 concentration in the actual cerebral blood flow, It cannot not be sure that an increase in rSO2 is real hyperoxia. Our study was limited in confirming the exact correlation between cerebral oximeter and PaO2 as a retrospective study. However, our results suggest that the possibility of neuronal damage due to increased oxygenation cannot be completely ruled out.

In conclusion, excessively increased cerebral oximeter values during major cardiac surgery may predict the development of POND. The increased cerebral oximeter value is considered to reflect the possibility of oxidative neuronal damage, and further studies are needed in the future.

Supporting information
S1 Table. Classification of POND.
(DOCX)

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References

1. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. The New England journal of medicine. 2001; 344(6):395–402. Epub 2001/02/15. https://doi.org/10.1056/NEJM200102083440601 PMID: 11172175.

2. Zimpfer D, Czerny M, Voigt F, Schuch P, Kramer L, Wolner E, et al. Neurocognitive deficit following coronary artery bypass grafting: a prospective study of surgical patients and nonsurgical controls. Ann Thorac Surg. 2004; 78(2):513–8; discussion 8–9. Epub 2004/07/26. https://doi.org/10.1016/j.athoracsur.2004.03.006 PMID: 15276509.

3. Brown CH. Delirium in the cardiac surgical ICU. Curr Opin Anaesthesiol. 2014; 27(2):117–22. Epub 2014/02/12. https://doi.org/10.1097/ACO.0000000000000061 PMID: 24514034; PubMed Central PMCID: PMC4156112.

4. Oliver CN, Starke-Reed PE, Stadtman ER, Liu GJ, Carney JM, Floyd RA. Oxidative damage to brain proteins, loss of glutamine synthetase activity, and production of free radicals during ischemia/reperfusion-induced injury to gerbil brain. Proc Natl Acad Sci U S A. 1990; 87(13):5144–7. Epub 1990/07/01. https://doi.org/10.1073/pnas.87.13.5144 PubMed Central PMCID: PMC54278. PMID: 1973301.

5. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med. 2017; 103:192–8. Epub 2017/01/01. https://doi.org/10.1016/j.freeradbiomed.2016.12.039 PMID: 28039082; PubMed Central PMCID: PMC5258679.

6. Scheeren TWL, Kuizenga MH, Maurer H, Struys M, Heringlake M. Electroencephalography and Brain Oxygenation Monitoring in the Perioperative Period. Anesthesia and analgesia. 2019; 128(2):265–77. Epub 2018/01/26. https://doi.org/10.1213/ANE.0000000000002812 PMID: 29369096.

7. Yu Y, Zhang K, Zhang L, Zong H, Meng L, Han R. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. Cochrane Database Syst Rev. 2018; 1 (1).Cd010947. Epub 2018/01/18. https://doi.org/10.1002/14651858.CD010947.pub2 PMID: 29341066; PubMed Central PMCID:PMC6491319 none known. Huantao Zong: none known. Lingzhong Meng: none known.

8. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg. 2007; 104(1):51–8. Epub 2006/12/21. https://doi.org/10.1213/ane.0000246814.29362.f4 PMID: 17179242.

9. Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. Journal of cardiothoracic and vascular anesthesia. 2004; 18(5):552–8. Epub 2004/12/04. https://doi.org/10.1053/j.jvca.2004.07.007 PMID: 15578464.

10. Higami T, Kozawa S, Asada T, Obo H, Gan K, Iwashiki K, et al. Retrograde cerebral perfusion versus selective cerebral perfusion as evaluated by cerebral oxygen saturation during aortic arch reconstruction. Ann Thorac Surg. 1999; 67(4):1091–6. Epub 1999/05/13. https://doi.org/10.1016/s0003-4875(99)00135-6 PMID: 10320256.
11. Zorrilla-Vaca A, Healy R, Grant MC, Joshi B, Rivera-Lara L, Brown C, et al. Intraoperative cerebral oximetry-based management for optimizing perioperative outcomes: a meta-analysis of randomized controlled trials. Can J Anaesth. 2018; 65(5):529–42. Epub 2018/02/11. https://doi.org/10.1007/s12630-018-1065-7 PMID: 29427259.

12. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB, Shotwell MS, et al. Intraoperative Oxidative Damage and Delirium after Cardiac Surgery. Anesthesiology. 2020; 132(3):551–61. Epub 2019/11/27. https://doi.org/10.1097/ALN.0000000000003016 PMID: 31770146; PubMed Central PMCID: PMC7015795.

13. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or restrictive transfusion after cardiac surgery. The New England journal of medicine. 2015; 372(11):997–1008. Epub 2015/03/12. https://doi.org/10.1056/NEJMoa1403612 PMID: 25760354.

14. Luger MF, Müller S, Kammerlander C, Gosch M, Luger TJ. Predictors of Postoperative Cognitive Decline in Very Old Patients With Hip Fracture: A Retrospective Analysis. Geriatr Orthop Surg Rehabil. 2014; 5(4):165–72. Epub 2015/08/08. https://doi.org/10.1177/215458514548577 PMID: 26246936; PubMed Central PMCID: PMC4252157.

15. Draelio LA, Racine AM, Yun Gou R, Marcantionio ER, Xie Z, Kunze LJ, et al. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. Anesthesiology. 2019; 131(3):477–91. Epub 2019/06/06. https://doi.org/10.1097/ALN.0000000000002729 PMID: 31166241; PubMed Central PMCID: PMC6692220.

16. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001; 286(21):2703–10. Epub 2001/12/26. https://doi.org/10.1001/jama.286.21.2703 PMID: 11730446.

17. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974; (2)(7872):81–4. Epub 1974/07/13. https://doi.org/10.1016/s0140-6736(74)91639-0 PMID: 4136544.

18. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002; 166(10):1338–44. Epub 2002/11/08. https://doi.org/10.1164/rccm.2107138 PMID: 12421743.

19. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics. 1996; 52(1):249–64. Epub 1996/03/01. PMID: 8934595

20. de Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. Journal of cardiothoracic and vascular anesthesia. 2011; 25(1):95–104. Epub 2010/07/24. https://doi.org/10.1053/j.jvca.2010.03.019 PMID: 20650659.

21. Holmgaard F, Vedel AG, Rasmussen LS, Paulson OB, Nilsson JC, Ravn HB. The association between postoperative cognitive dysfunction and cerebral oximetry during cardiac surgery: a secondary analysis of a randomised trial. Br J Anaesth. 2019; 123(2):196–205. Epub 2019/05/21. https://doi.org/10.1016/j.bja.2019.03.045 PMID: 31104758; PubMed Central PMCID: PMC6676044.

22. Abramson NS, Safar P, Detre KM, Kelsey SF, Monroe J, Reinmuth O, et al. Neurologic recovery after cardiac arrest: effect of duration of ischemia. Brain Resuscitation Clinical Trial I Study Group. Crit Care Med. 1985; 13(11):930–1. Epub 1985/11/01. PMID: 4053643

23. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest: a study in healthy volunteers using magnetic resonance phase-contrast angiography. European journal of anaesthesiology. 2000; 17(3):2717–22. Epub 2001/05/25. https://doi.org/10.11161/CIRCULATIONAHA.110.001016 PMID: 21606393.

24. Hazeltin JL, Balan I, Elmer GI, Kristian T, Rosenthal RE, Krause G, et al. Hyperoxic reperfusion after global cerebral ischemia promotes inflammation and long-term hippocampal neuronal death. J Neurotrauma. 2010; 27(4):753–62. Epub 2010/01/12. https://doi.org/10.1089/neu.2009.1186 PMID: 20059303; PubMed Central PMCID: PMC2867550.

25. Watson NA, Beards SC, Altal N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. European journal of anaesthesiology. 2000; 17(3):152–8. Epub 2000/04/12. https://doi.org/10.1016/j.1365-2346.2000.00640.x PMID: 10758463.

26. Fessel JP, Porter NA, Moore KP, Sheller JR, Roberts LJ 2nd. Discovery of lipid peroxidation products formed in vivo with a substituted tetrahydrofuran ring (isofurans) that are favored by increased oxygen tension. Proc Natl Acad Sci U S A. 2002; 99(26):16713–8. Epub 2002/12/17. https://doi.org/10.1073/pnas.252649099 PMID: 12482927; PubMed Central PMCID: PMC139209.
27. Liu Y, Rosenthal RE, Haywood Y, Miljkovic-Lolic M, Vanderhoek JY, Fiskum G. Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. Stroke. 1998; 29(8):1679–86. Epub 1998/08/26. https://doi.org/10.1161/01.str.29.8.1679 PMID: 9707212

28. Hou X, Roberts LJ 2nd, Gobeil F Jr., Taber D, Kanai K, Abran D, et al. Isomer-specific contractile effects of a series of synthetic f2-isoprostanes on retinal and cerebral microvasculature. Free Radic Biol Med. 2004; 36(2):163–72. Epub 2004/01/28. https://doi.org/10.1016/j.freeradbiomed.2003.10.024 PMID: 14744628.

29. Arendash GW, Cox AA, Mori T, Cracchiolo JR, Hensley KL, Roberts LJ, 2nd. Oxygen treatment triggers cognitive impairment in Alzheimer’s transgenic mice. Neuroreport. 2009; 20(12):1087–92. Epub 2009/06/23. https://doi.org/10.1097/WNR.0b013e32832e6459 PMID: 19543132.

30. Harker LA, Malpass TW, Branson HE, Hessel EA, 2nd, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. Blood. 1980; 56(5):824–34. Epub 1980/11/01. PMID: 6448643

31. Whitlock R, Crowther MA, Ng HJ. Bleeding in cardiac surgery: its prevention and treatment—an evidence-based review. Crit Care Clin. 2005; 21(3):589–610. Epub 2005/07/05. https://doi.org/10.1016/j.ccc.2005.04.003 PMID: 15992674.

32. Salonia R, Bell MJ, Kochanek PM, Berger RP. The utility of near infrared spectroscopy in detecting intracranial hemorrhage in children. J Neurotrauma. 2012; 29(6):1047–53. Epub 2011/11/22. https://doi.org/10.1089/neu.2011.1890 PMID: 22098538; PubMed Central PMCID: PMC3325547.

33. Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, et al. Delirium accelerates cognitive decline in Alzheimer disease. Neurology. 2009; 72(18):1570–5. Epub 2009/05/06. https://doi.org/10.1212/WNL.0b013e3181a4129a PMID: 19414723; PubMed Central PMCID: PMC2677515.